Early and locally advanced breast cancer (update)

Consultation on draft guideline - Stakeholder comments table
24/01/2018 to 06/03/2018

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Association of Breast Surgery	Draft	General	General	'Risk can be estimated using a range of standardised tools and clinical expertise' is used throughout the document. Probably ok for 'high risk' of invasive disease in DCIS BCS patients who may be offered SNB. However, for adjuvant endocrine, bisphosphonates, etc. it just means that everyone can interpret this differently and will have to battle individually with local commissioners. I know they've recommended research for bisphosphonates but some definitions would be helpful.	Thank you for your comment. We agree that using this phrase allows for different interpretation of what is low, medium and high risk and for some of the recommendations (1.7.6.and 1.7.7) we amended the footnote to define what is meant by high and low risk in more detail. However, the committee agreed that it was not possible to define risk consistently across the guideline and that treatment should be individualised based on a number of factors including specific details of the tumour, the stage in treatment, the response to treatment so far, patient-related factors and comorbidities. Therefore risk can only be assigned to individual people after discussion with their clinician. In order to encourage these discussions however, and to provide more information on the likely risks and benefits and how they should be balanced for different treatment options we have included a number of preference sensitive decision point tables within the guideline.
Association of Breast Surgery	Draft	General	General	NICE do not mention genomic testing to guide the benefit of chemotherapy at all in this guidance. This is a big omission.	Thank you for your comment. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on tumour profiling tests to guide adjuvant therapy decisions [Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10)].

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Association of Breast Surgery	Draft	5	21	1.3.2 This is a vague comment that will not help MDTs across the country	Thank you for your comment. There was insufficient evidence found to make a stronger recommendation in this group of people and the committee agreed that this discussion would currently be held at an MDT and a decision would be made on an individual patient basis, and that this practice should continue.
Association of Breast Surgery	Draft	7	8-16	1.4.7 & 1.4.8 The wording of these two entries is confusing and may be misread to contradict each other. Entry 1.4.7 could be improved by simply changing the word "offer" to "consider" and this would seem less contradictory to 1.4.8	Thank you for your comment. There was evidence in support of axillary treatment for those with pathologically proven involvement of axillary sentinel lymph nodes, the population referred to in 1.4.7 ('people who have 1 or more sentinel lymph node macrometastases') which allowed the committee to make an offer recommendation. But there were unclear benefits and risks of further axillary treatment for the lower risk subgroup in 1.4.8 with 1 or 2 sentinel lymph nodes who had also been advised to have whole breast radiotherapy and systemic therapy. While the subgroup in 1.4.8 would also be offered further axillary treatment the risks and benefits of no further axillary treatment should also be discussed as an option (ideally as part of a clinical trial).
Association of Breast Surgery	Draft	7	11-16	1.4.8 ABS believes that the following should be added: In women who have 1 or 2 sentinel lymph node macrometastases and are treated by mastectomy *and* who have been advised to have systemic therapy (which may be endocrine therapy), no further axillary treatment could be considered within the context of a clinical trial.	Thank you for your comment. None of the evidence came from trials where mastectomy was the only primary treatment (although in some trials both mastectomy and breast conserving therapy were options) so the committee could not make a specific recommendation for the mastectomy group. However, the guideline makes a general recommendation about inclusion into trials (1.2.4) and therefore inclusion into a trial could be discussed as part of any of the recommendations, where appropriate.
Association of Breast Surgery	Draft	10	9-21, 1-22,1-9	1.7	Thank you for your comment. There was insufficient evidence found to make a recommendation on the

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				There should be a statement from NICE on use of extended endocrine therapy in postmenopausal women who have been taking an aromatase inhibitor for 5 years.	extension of endocrine therapy in women who had been taking an aromatase inhibitor for 5 years.
Association of Breast Surgery	Draft	15,19	20-23, 1-27, 1-21, 1-23, 1-7	1.10 Presume they will add something in about IORT or signpost - NICE recommendations came out after draft circulated.	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.
Association of Breast Surgery	Draft	16	1-3	1.10.2 A clear definition of "low absolute risk of local recurrence" is presented in this section. However, throughout the guidance NICE states that "Risk can be estimated using a range of standardised tools and clinical expertise".	Thank you for your comment. Where possible, and where there was good evidence that allowed the specific sub-groups to be detailed, the committee included this information. However, this was not possible for all the recommendations where a broader definition of risk and how it should be assessed had to be used.
Association of Breast Surgery	Draft	17	17-19	1.10.10 There is concern that a blanket recommendation for post-mastectomy radiotherapy may represent over treatment for those patients with 1-3 lymph node positivity.	Thank you for your comment. The committee agree that this may represent over-treatment and that future data from the SUPREMO trial may help address this. However, subsequent recommendations do define the populations in more detail, and allow the option of not carrying out postmastectomy radiotherapy in those with low risk. The evidence available to the committee did not allow a distinction to be made for the benefit of radiotherapy in people with 1 to 3 positive nodes, compared to those with 4+ positive nodes. Reduced loco-regional recurrence was seen in women with 1 to 3 positive nodes who were given radiotherapy, even when the tumour size was small (0 to 19 mm), and there was no difference in magnitude of this effect compared with medium or larger tumours. Furthermore, the magnitude of difference seen with radiotherapy in the evidence reviewed by the committee

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					was not smaller for 1-3 nodes (14% difference in recurrence, RR=0.24) compared to 4+ nodes (11% difference in recurrence, RR=0.39)
Association of Breast Surgery	Draft	21	4-9	1.11.11 & 1.11.13 It is not clear what is meant by "post surgical investigations"	Thank you for your comment. The wording of this recommendation has been changed to 'histology' to make this clearer.
Breast Cancer Care	General	General	General	**Fertility discussions and access to fertility services** In our response to the scoping stage of this update we highlighted a need for the updated guideline to include reference to fertility issues for people treated for breast cancer. This is still an issue which we are calling to be addressed in this update. This topic would best sit in section **1.1 Referral, diagnosis and preoperative assessment**. Breast Cancer Care is aware that people diagnosed with breast cancer are often not having discussions with their healthcare professionals about options to preserve their fertility before their treatment starts. In February 2018, Breast Cancer Care conducted a patient survey* into this area. We received responses to our survey from 254 women diagnosed with breast cancer under the age of 45, who kindly shared their experiences. We found that there is a high proportion of women whose healthcare professionals did not discuss fertility options with them. 21% of women said that they did not have such a discussion. This is despite recommendations in NICE Clinical Guideline 156: *Fertility Problems: Assessment and Treatment* that, '*At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team'.*	Thank you for your comment. The management of fertility issues and access to fertility services was not prioritised for investigation in this guideline, but, as you suggested, a cross-reference to the NICE guideline on the assessment and management of fertility problems (CG156) has been included in section 1.2 Information and support. This fertility guideline includes a section on people with cancer who wish to preserve their fertility. Inclusion of this link will increase awareness for all those reading this guideline, both people with cancer and healthcare professionals, about the need to consider fertility issues when providing information and support to people with breast cancer

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				Of the 21%, some women who were aware of the potential impact of treatment on their fertility did raise this with their healthcare professional themselves. However, many found this challenging: *'When I asked about having children I was made to feel like I was wasting their time and basically ignored as they felt not important.'* Another person told us: *'I had to ask about fertility and push to have my eggs frozen before treatment started.'* Of course, not all patients will be as aware of the potential impact of treatment on their fertility and/or be confident to raise this issue unprompted. Ensuring that guidance is available for healthcare professionals within the updated Early and Locally Advanced Breast Cancer Guideline is therefore vital. Of those who did say they had a discussion with their healthcare professional, many did not find this a positive experience, again highlighting the need for specific guidance on this in the updated guideline: *'I was simply assured that I would be able to have more children but not given any other information. After treatment I felt there was a bit of backtracking when I asked about fertility, then it was "well you have a good chance of being able to have children.'* Another person told us: *'It was mentioned but glossed over in the rush to start chemo.'*	

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				Some respondents commented on unhelpful assumptions made by healthcare professionals, which meant that they missed out on opportunities to discuss fertility further: *'I'm in a same sex relationship and it was unfortunately overlooked by my team. I had to ask about fertility treatment as when initially diagnosed and advised I would be having chemo. This was later reversed due to the Oncotype test but they just assumed fertility was not an issue for me being in a same sex relationship which I found very upsetting.'* Our survey also found that referrals to a fertility specialist are very patchy. 42% of respondents to our survey were not offered a referral to a fertility specialist. Breast Cancer Care wants to see every breast clinic have a process for referring women promptly to a fertility specialist. This referral shouldn't depend on local in vitro fertilisation (IVF) funding arrangements. Those who did have a fertility discussion and were also referred to a fertility specialist told us of the positive impact this had on their overall treatment and care: *'I was offered fertility treatment after my lumpectomy and before I started chemo. I was provided a lot of information by [my hospital], where I received my fertility treatment. [My hospital] gave me brilliant service and care, they were amazing. It was quick and painless for me. I had 20 eggs taken and 18 successfully stored.'*	

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				'I had a fantastic experience - my surgeon discussed fertility treatment and referred me without me even mentioning that it was an area of concern. It's appalling that this isn't the default level of treatment for all women!' We feel that these findings confirm the need for this issue to be specifically addressed in the updated Early and Locally Advanced Breast Cancer Guideline. As stated in our response to the scoping consultation, Breast Cancer Care would like to see recommendations in the updated guideline along the lines of: 1. People diagnosed with breast cancer should be able to discuss the possible effects of treatment on their fertility and future pregnancies, and how likely this is, before treatment starts. 2. People diagnosed with breast cancer should be offered a prompt referral to a fertility specialist, whether they have a partner or not, to discuss options for trying to preserve fertility before starting chemotherapy or hormone treatment. At the very least, the updated guideline should signpost healthcare professionals to the NICE guideline *Fertility Problems: Assessment and Treatment* (Clinical Guideline 156). This would address the lack of guidance currently. --- *Survey undertaken online by Breast Cancer Care between 22 February and 1 March 2018. Total sample size: 254 women.	

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				For further information about this survey, please contact Breast Cancer Care.	
Breast Cancer Care	Draft	5	9	**Providing information and psychological support** <u>Recommendation 1.2.1</u> Breast Cancer Care is concerned about the change in recommendation 1.2.2 from the term 'breast care nurse specialist' to 'named key worker'. Although this area is listed as an area in which NICE is not inviting comments, this is a significant change in terminology that we have concerns about. The term 'key worker' is vague. However, broadly speaking the distinction between a key worker and specialist role is as follows: **Specialist role** – A breast-cancer specialist role undertaken by a registered nurse, who holds specialist expertise in breast cancer treatment and management. Includes roles such as a Clinical Nurse Specialist. **Key worker role** – Typically a non-specialist role, not usually a registered nurse, who provides care coordination, education and self-management support for patients with care needs assessed as non-complex. We are concerned that changing this recommendation could therefore lead to patients missing out on this specialist support.	Thank you for your comment. This recommendation has now been amended to state that people 'should have a named clinical nurse specialist or other specialist key worker with equivalent skills'. This reflects the fact that the committee recognised that people should have access to someone with the appropriate clinical knowledge and skills to support them, but that did not necessarily always have to be a nurse.

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				The value and importance of a specialist nursing roles is well-documented. The National Cancer Patient Experience Survey for England shows that patients who have been allocated a CNS are more positive about their experience of care. There is value in having a non-nurse key worker to support the work of breast cancer specialist roles such as CNSs. They can reduce the administrative burden placed on the CNS, allowing them more time to spend supporting their patients. However, a non-nurse key worker role should not be recommended in place of a breast care nurse specialist.	
Breast Cancer Care	Draft	5	14	**Providing information and psychological support** Recommendation 1.2.4 For recommendation 1.2.4, we feel it would be helpful to clarify what is meant by 'support entry into clinical trials'. This needs to be clarified or expanded to provide meaningful guidance.	Thank you for your comment. The committee were aware that for a number of the areas included in the guideline there was ongoing research that would provide evidence to support or change practice, or in areas where there is currently very little or no evidence. The committee therefore chose to make an over-arching recommendation at the beginning of the guideline to support entry into clinical trials for all people where appropriate, to increase the evidence base and further support evidence-based practice. In light of your comment we have changed this to '…encourage entry…' as this provides a clearer role for healthcare professionals and requires them to be more pro-active.
Breast Cancer Care	Draft	5	18	**Surgery to the breast** Recommendation 1.3.1 We would suggest strengthening this recommendation by replacing the term 'offer' with 'recommend' further surgery given the importance of achieving clear margins for reducing the	Thank you for your comment. 'Offer' is the term used in NICE guidelines to indicate a strong recommendation and can be considered to be synonymous with 'recommend'.

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				likelihood of recurrence. It seems incongruous that something which is evidence-based and should be routine practice is cited as 'offer'.	
Breast Cancer Care	Draft	8	2-16	**Breast reconstruction** Contralateral symmetry surgery is not mentioned in this section, yet is relevant to the outcomes of, and satisfaction with, breast reconstruction. Does recommendation 1.5.3 'all appropriate reconstruction options' include this?	Thank you for your comment. The committee did not specifically consider the evidence for contralateral symmetry procedures, but we have added wording to the rationale and impact discussion about the importance of symmetry, so second mastectomy should be discussed as part of a consideration of breast reconstruction options to allow for symmetry.
Breast Cancer Care	Draft	9	7	**Diagnostic assessment and adjuvant therapy planning - Predictive factors** Recommendation 1.6.5 In practice, we know that a patient's HER2 status is not routinely available at the multidisciplinary team (MDT) meeting or at the post-operative results visit, and that patients often have to wait for this. The rationale given for having HER2 status available at the MDT meeting – that this will avoid delays and the need for additional discussions (p.31, line 26) – is not necessarily true. In practice, patients often wait longer for the MDT discussion and subsequent results appointment. This wait is sometimes up to 4 weeks post-op. As the 30 day treatment target clock starts ticking from this appointment, in reality patients can wait up to 8 weeks to start adjuvant treatment.	Thank you for your comment. The committee agreed that the ER, PR and HER2 status should be requested at the time of initial histopathological diagnosis (recommendation 1.6.1) and we have amended recommendation 1.6.5 to make it clear that the results should be available at the pre-operative and postoperative multidisciplinary team meetings to avoid delays.
Breast Cancer Care	Draft	9	21	**Diagnostic assessment and adjuvant therapy planning - adjuvant therapy planning**	Thank you for your comment. Recommendation 1.6.9 which describes the limitations of PREDICT has been

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				Recommendation 1.6.9 The groups listed for 'with caution' use (those over 70 and HER2+) represent high proportions of the patient population, so more explanation for clinicians of why the PREDICT tool should be used with caution is needed here as it is not entirely clear what this means in practice. This is especially important as genomic tests are now not recommended, meaning there are no alternatives for clinicians to use.	amended to make this clearer, and to highlight in which sub-groups PREDICT may be less accurate, and in which groups the validation has not been carried out.
Breast Cancer Care	Draft	10	14	**Endocrine therapy - adjuvant endocrine therapy for invasive breast cancer** Although this area is listed as an area in which NICE is not inviting comments, we have comments which we would like to make. **Recommendation 1.7.2** This recommendation appears to contradict the guidance in recommendations 1.7.4 and 1.7.5 – that is, to offer tamoxifen in premenopausal women, but then also consider ovarian suppression and aromatase inhibitors.	Thank you for your comment. The adjuvant endocrine therapy for invasive breast cancer recommendations within the guideline were not prioritised for this guideline update, and no evidence was reviewed so we are unable to change this recommendation. However, the committee do not believe 1.7.2 is contradicted by 1.7.4 and 1.7.5 as 1.7.4 and 1.7.5 suggest additional therapy in a particular sub-group of women.
Breast Cancer Care	Draft	10	14	**Endocrine therapy – ovarian function suppression** Recommendation 1.7.4	Thank you for your comment. There was no evidence for different age groups so we are unable to add this to the recommendation.

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				Would adding an age limit to this recommendation be useful for clarity?	
Breast Cancer Care	Draft	11	11-22	**Endocrine therapy - extended endocrine therapy** <u>Recommendations 1.7.6 – 1.7.8</u> These recommendations refer only women with ER-positive breast cancer. Clarity is needed on whether to treat patients with other types of breast cancer (ER-negative, PR+) with endocrine therapy. Currently this is inconsistency on this UK wide.	Thank you for your comment. The review did not include looking for evidence of benefit in people with ER-negative, PR-positive breast cancer so the committee were unable to make recommendations for this sub-group.
Breast Cancer Care	Draft	11	11	**Endocrine therapy - extended endocrine therapy** <u>Recommendation 1.7.6</u> We feel that the phase 'offer extended therapy (total duration of endocrine therapy of more than 5 years)' is too vague. More guidance is needed. Evidence suggests that 7-8 years is enough and 10 may not be needed. A study by Gnant et all* concluded that women who took anastrozole for two years after initial adjuvant endocrine therapy received an equal benefit to those who took the drug for a further five years. Therefore there is no basis to keep most postmenopausal women on extended AIs for longer than 2 years after initial adjuvant therapy. --- *Gnant M, Steger G, Greil R, et al. *A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years*	Thank you for your comment. The focus of the review question was to compare durations of greater than 5 years against 5 years of endocrine therapy; direct comparisons between durations beyond 5 years were not made. However, there was no clear pattern of results based on the durations of the included studies so the committee did not think it was possible to make recommendations on the absolute duration of therapy or endpoint. We are aware that there are ongoing studies in this area but there was insufficient data in this abstract to allow us to include it in the evidence review.

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				of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, TX. Abstract GS3-01.	
Breast Cancer Care	Draft	11	20	**Endocrine therapy - extended endocrine therapy** Recommendation 1.7.8 We feel that the wording of this recommendation ('*Consider extending the duration of tamoxifen therapy for longer than 5 years*') is too vague. More guidance is needed on the reasons why clinicians might consider extending tamoxifen for longer than 5 years. The rationale given for including this new recommendation states that '*the evidence showed no benefit in terms of disease-free survival or overall-survival from continuing tamoxifen beyond 5 years. However, some of the studies on tamoxifen were conducted in the 1980s and may not be relevant to current practice. In the committee's experience, continuing tamoxifen can be beneficial for some women'* (page 33, lines 19-23). The section also talks about potential problems associated with taking endocrine therapy for more than 5 years, and the need for healthcare professionals to discuss the potential benefits and risks with women to help them make an informed choice about treatment. Taking this into account, we feel that the importance of discussion with the patient should be better reflected in this recommendation.	Thank you for your comment. The committee agreed that there was enough evidence of benefit to extend therapy with tamoxifen, but appreciated the risks and side-effects associated with this too, and a preference sensitive decision point table has been included in the guideline to assist with the discussion of risks and benefits of extended endocrine therapy.

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Breast Cancer Care	Draft	12	2-6	**Endocrine therapy for ductal carcinoma in situ** Recommendations 1.7.9 and 1.7.10 No duration of tamoxifen is cited. This is inconsistent with the section on invasive breast cancer and requires clarification.	Thank you for your comment. There was no evidence available to the committee on different durations of therapy for DCIS so it was not possible to make recommendations on the absolute duration of therapy or endpoint.
Breast Cancer Care	Draft	12	2	**Endocrine therapy for ductal carcinoma in situ** Recommendation 1.7.9 This recommendation only mentions offering endocrine therapy after breast-conserving surgery. Clarification is needed as to whether those patients who have had a mastectomy for ER-positive DCIS should also receive endocrine therapy.	Thank you for your comment. There was no evidence available to the committee on the use of endocrine therapy after mastectomy for DCIS, so the committee were unable to make any recommendations for this group of people.
Breast Cancer Care	Draft	14	16-21	**Bisphosphonate therapy - adjuvant bisphosphonate therapy** Recommendations 1.9.1 and 1.9.2 Clarification is needed as to the duration for which bisphosphonates should be given.	Thank you for your comment. The duration of therapy was not included in the evidence review for adjuvant bisphosphonates so the committee were unable to make any recommendations on this. Furthermore, the EBCTG meta-analysis did not find enough evidence to recommend a specific duration of therapy either.
Breast Cancer Care	Draft	14	16-21	**Bisphosphonate therapy - adjuvant bisphosphonate therapy** Recommendations 1.9.1 and 1.9.2 It is not clear from the recommendations whether they apply to women who are post-menopausal as a result of their treatment for breast cancer. It would be helpful to clarify this.	Thank you for your comment. The use of bisphosphonates in natural menopause versus treatment-related menopause was not included in the evidence review for adjuvant bisphosphonates so the committee were unable to make any recommendations on this.

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Breast Cancer Care	Draft	14	9	**Adjuvant chemotherapy for invasive breast cancer - biological therapy** Recommendation 1.8.8 Clarification is needed as to whether trastuzumab can be given without chemotherapy. In the rationale for this recommendation, it states that: '*the committee agreed that it was more appropriate to offer combined chemotherapy and trastuzumab'.* However, this is not reflected in the recommendation.	Thank you for your comment. Trastuzumab is licensed to be given in addition to chemotherapy, and the wording of the recommendation has been amended to refer to the use of chemotherapy.
Breast Cancer Care	Draft	16	15-17	**Radiotherapy - radiotherapy after breast conserving surgery** Recommendation 1.10.4 This recommendation does not mention intraoperative radiotherapy, which has been recommended by NICE* (although not for routine commissioning). --- * NICE Technology Appraisal 501, *Intrabeam radiotherapy system for adjuvant treatment of early breast cancer,* 2018, available at: https://www.nice.org.uk/guidance/ta501 [accessed 21.02.2018]	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy, as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.
Breast Cancer Care	Draft	23	9	**Complications of local treatment and menopausal symptoms - menopausal symptoms** Recommendation 1.12.12	Thank you for your comment. The proposal not to include the menopause symptoms section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are only able to make

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				Although this area is listed as an area in which NICE is not inviting comments, we believe it implies SSRIs are the only pharmacological option. Omission of any reference to others such as gabapentin and clonidine will result in uncertainty about their use and does not reflect clinical practice.	minor changes to the wording and not changes which alter the meaning, so we are not able to make the changes that you suggest.
Breast Cancer Care	Draft	24	5-15	**Clinical follow-up** <u>Recommendation 1.13.4</u> Although this area is listed as an area in which NICE is not inviting comments, we feel strongly that an update is needed. In our response to the scoping stage of this update, we highlighted the lack of guidance in the current version of the guideline on informing patients of the signs and symptoms of secondary (metastatic) breast cancer. In the **Clinical follow-up** section, the current version of the guideline refers to giving patients information on '*signs and symptoms to look out for and seek advice on'* within a written care plan. We would emphasise the need for the guideline to include specific and clear guidance for healthcare professionals about informing patients specifically about signs and symptoms which could be indicative of secondary breast cancer. This will help ensure a quick diagnosis. While a prompt diagnosis may not lead to a different clinical outcome for the patient, it's important that people are diagnosed quickly for a number of reasons, including:	Thank you for your comment and for expressing your concerns about the need for people with breast cancer to receive information on the signs and symptoms of secondary breast cancer. We will pass this suggestion onto the NICE surveillance team who review evidence which may lead to guidelines requiring updating. However, the proposal not to include the clinical follow-up section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.

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				• starting treatment sooner with a view to lengthening periods of progression-free survival • improving quality of life • reducing the chances of serious complications from the cancer such as spinal cord compression At Breast Cancer Care we know that many people with a secondary breast cancer diagnosis were unaware of the signs and symptoms of secondary disease. Findings from a Breast Cancer Care patient survey of over 800 people with a diagnosis of secondary breast cancer* found that only 22% of patients with a diagnosis of secondary breast cancer said they knew how to spot the signs and symptoms of secondary disease. This highlights that sufficient information about this was not being provided to patients when they received follow-up care for their primary breast cancer. Compounding this problem is the lack of support for GPs in recognising the signs and symptoms of secondary breast cancer. 21% of survey respondents who had a previous primary breast cancer diagnosis were initially incorrectly treated for another condition before their secondary breast cancer was finally diagnosed. Both these issues mean that the possibility of earlier recognition and diagnosis is being missed on two fronts: 1) Patients themselves are not recognising the signs and symptoms of secondary breast cancer 2) GPs are not picking up potential cases of secondary breast cancer	

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				Unfortunately, we also found that 8% of people were diagnosed after they were seen as an emergency/A&E patient, suggesting that the signs and symptoms of secondary breast cancer were not recognised earlier. It is therefore vital that guidance is improved in this area, as guidance on informing patients (and GPs) of symptoms which could be indicative of secondary (metastatic) breast cancer is not currently covered in any other guidance, including Clinical Guideline 81, *Advanced Breast Cancer: Diagnosis and Treatment*, or NICE Guideline 12, *Suspected Cancer: Recognition and Referral.* --- * Breast Cancer Care (2016), Secondary. Not Second Rate. Part one: diagnosis, available at: https://www.breastcancercare.org.uk/sites/default/files/secondary-breast-cancer-report-part-1.pdf [accessed 21/02/2018]	
Breast Cancer Care	Draft	24	17-25	**Lifestyle** Recommendation 1.14.1 and 1.14.2 We feel that the term 'a healthy lifestyle' is not specific enough and requires more clarity.	Thank you for your comment. We have amended the wording of this recommendation to clarify that a healthy lifestyle encompasses achieving and maintaining a healthy weight, regular physical activity and limiting alcohol intake. The committee were aware that a healthy lifestyle can include other factors as well (such as smoking cessation) and have also added a recommendation that includes a link to the NICE guideline on stop smoking interventions and services.
Breast Cancer Care	Draft	24	17-25	**Lifestyle** Recommendation 1.14.1 and 1.14.2	Thank you for your comment. The committee had evidence that a limited alcohol intake was associated with a reduced recurrence, and the evidence for achieving and maintaining a healthy weight was based on evidence from

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				The rationale section for these recommendations mentions the impact of alcohol and fat intake on breast cancer survival and recurrence. This is an area of high confusion and concern, and there are still some unknowns: • Whether obesity effects breast cancer outcomes differently in HR-positive and negative disease. • There's insufficient evidence that weight loss and physical activity alter breast cancer specific mortality. Associations seen in observational studies may not be causal and there may be confounding factors such as under-treatment of obese patients or later diagnosis. • Lifestyle changes may not improve breast cancer outcomes for some because of the inherent biological aggressiveness of obesity-associated breast cancers or if the magnitude of feasible change is insufficient. Only randomised controlled trials will provide the definitive answer.	diets with a reduced fat content. There was no subgroup evidence available to the committee based on receptor status so the committee were unable to make any recommendations relating to HER2-positive and negative disease. The evidence review focussed on the risk of recurrence of breast cancer, not on mortality, and the committee were aware that associations may not be causal, and so used the expression 'associated with' in their recommendations. The committee agreed that there is limited evidence for the effects of lifestyle changes on breast cancer outcomes but also agreed that randomised controlled trials may be impractical or not ethical.
Breast Cancer Clinical Expert Group	Draft	General	General	The Breast Cancer Clinical Expert Group (CEG) published the Clinical Advice for the Provision of Breast Cancer Services to Cancer Alliances in August 2017.[1] We were asked to produce this by NHS England, who have endorsed the Clinical Advice and circulated it to Cancer Alliances in England.	Thank you for your comment and for sending details of the work of the Breast Cancer Clinical Expert Group on the Provision of Breast Cancer Services.

[1] Breast Cancer Clinical Expert Group, 2017. Clinical Advice for the Provision of Breast Cancer Services to Cancer Alliances. Available from: http://breastcancernow.org/sites/default/files/public/clinical_advice_for_the_provision_of_breast_cancer_services_aug_2017.pdf

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				The Breast Cancer CEG has a wide geographical and multi-disciplinary representation from the full range of professionals involved in delivering breast cancer services, as well as patient representatives and groups. The Clinical Advice gives a summary of best practice covering essential services for early, locally advanced and metastatic breast cancer. This whole pathway approach is intended to aid the commissioning of local and national breast cancer services. We will refer to the Clinical Advice in our response.	
Breast Cancer Clinical Expert Group	Draft	5	9	We are concerned about the recommendation 1.2.3 changing from access to a Clinical Nurse Specialist (CNS) to "access to a key worker". In the Clinical Advice for Breast Cancer patients that has been endorsed by NHS England, we recommend that "All patients must have access to a clinical nurse specialist **at all stages in their treatment pathway**".[2] Analysis of the Cancer Patient Experience Survey data shows that the single most important factor associated with high patient scores is the patient being given the name of a clinical nurse specialist in charge of their care.[3] While we understand pilots are underway in Cancer Alliances to test the key worker model, this role has not been defined and we believe best practice should dictate that where possible this is a Clinical Nurse Specialist. We would urge this to read at the very	Thank you for your comment. This recommendation has now been amended to state that people 'should have a named clinical nurse specialist or other specialist key worker with equivalent skills'. This reflects the fact that the committee recognised that people should have access to someone with the appropriate clinical knowledge and skills to support them, but that did not necessarily always have to be a nurse.

[2] Breast Cancer Clinical Expert Group, p.9
[3] NHS England, 2017. National Cancer Patient Experience Survey 2016. Available at: http://www.ncpes.co.uk/reports/2016-reports/national-reports-1/3572-cpes-2016-national-report/file

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				minimum "access to a CNS, or other key worker" to encourage best practice in most places.	
Breast Cancer Clinical Expert Group	Draft	7	8-10	Recommendation 1.4.7 goes against ABS Guidelines[4] and Z11 10 year trial results.[5] Despite the fact we recognise some flaws in this trial, evidence suggests that no further treatment should be considered.	Thank you for your comment. The committee were aware of the Association of Breast Surgeons guidelines, but this is a consensus document and the recommendation 1.4.7 is based on the evidence review conducted for this guideline. Furthermore, the committee did not believe the recommendations contradicted this document. Although the ACOSOG Z0011 10 year trial results support no further axillary treatment for people with macrometastatic disease, the committee decided against routinely recommending this approach due to risk of bias in that trial. In particular recruitment bias due to participants being randomised after the sentinel lymph node results were known, radiotherapy treatment fields being altered in people randomised to have ALND and some patients being given radiotherapy off protocol, as well as attrition bias because data for long-term complications were only available for a subset of participants.
Breast Cancer Clinical Expert Group	Draft	7	12	We are concerned that the wording of recommendation 1.4.8 excludes patients who choose to have a mastectomy from entering into the POSNOC trial, the only clinical trial on offer for the evaluation and management of positive axillary lymph node. We would advise the wording to change to: "after primary ~~breast-conserving~~ surgery (within clinical trials where available) with women who:	Thank you for your comment. There was no evidence from trials where the primary treatment was exclusively mastectomy so the committee could not make a specific recommendation for this group, but this recommendation does not exclude entry into the POSNOC trial. However, the guideline makes a general recommendation abut inclusion into trials (1.2.4) and therefore inclusion into a

[4] Association of Breast Surgeons, 2015. Association of Breast Surgery Consensus Statement: Management of the Malignant Axilla in Early Breast Cancer. Available from: https://associationofbreastsurgery.org.uk/media/1436/management-of-the-malignant-axilla-in-early-breast-cancer.pdf

[5] Guiliano et al, 2017. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. Available from: https://jamanetwork.com/journals/jama/article-abstract/2653737?redirect=true

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				- have 1 or 2 sentinel lymph node macrometastases **and** **-** have been advised to have whole breast radiotherapy with systemic therapy (which may be endocrine therapy)"	trial could be discussed as part of any of the recommendations, where appropriate.
Breast Cancer Clinical Expert Group	Draft	8 AND 31	15-16, 3-13	We agree with recommendation 1.5.3 that all methods of reconstruction should be discussed even if not locally available. In the 'why have we said this' section and in particular on 'how this recommendation affect practice' we know that many surgeons currently would not genuinely discuss DIEP flap as it might not be available locally but for many might be the best option for an immediate reconstruction. Current practice is that the overwhelming majority of patients have primary implant reconstruction. If autologous reconstruction and DIEP flap was discussed with all - which we agree should be the case – it should be considered that it might have a considerable effect on the availability of this service (which is already inadequate) and result in treatment delay.	Thank you for your comment and support for this recommendation. One of the aims of NICE guidelines is to ensure equity of availability of services across the NHS, and the committee recognised that all options should be offered, even if they are not available locally. The implementation of the guideline should therefore lead to improvements in access and availability through changes in commissioning.
Breast Cancer Clinical Expert Group	Draft	8	20	We are happy to see that the progesterone receptor (PR) will also be recognised as a clinically relevant prognostic factor in recommendation 1.6.1.	Thank you for your comment and support for the inclusion of the progesterone receptor assay in this recommendation.
Breast Cancer Clinical Expert Group	Draft	9	7-9	For recommendation 1.6.5 we would like to see a small change in the wording of this. The guidelines recommend that the receptors should be available before discussion of systemic therapy, which allows people to have these available for the post-operative multi-disciplinary team (MDT) meeting but not necessarily the pre-operative MDT. We would like this to be made more explicit so that ER, PR and Her2 are available at the pre-operative MDT so that neoadjuvant therapy can be considered where appropriate.	Thank you for your comment. We have amended this recommendation to make it clear that the results should be available at the pre-operative and postoperative multidisciplinary team meeting.
Breast Cancer	Draft	9	19-20	In recommendation 1.6.8 we believe that PREDICT tool is a poor substitution for the genomic platforms that are currently in use –	Thank you for your comment. Consideration of genomic testing was not prioritised for this guideline update as it

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Clinical Expert Group				such as Oncotype DX- in determining who will, and more importantly who will NOT, achieve significant clinical benefit from adjuvant chemotherapy. (For transparency, Prof Ian Smith, Chair of Breast CEG, wishes it to be noted that he sits on a Genomic Health Advisory Group). Other platforms should be reconsidered in the breast diagnostics guidelines.	has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on tumour profiling test to guide adjuvant therapy decisions [Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10)}.
Breast Cancer Clinical Expert Group	Draft	11	10-22	There is no mention of extended endocrine therapy after 5 years of aromatase inhibitors, only after 2-5 years of tamoxifen in recommendations 1.7.6 and 1.7.8. The study "Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years."[6] has been excluded on the grounds of the "Comparison out of scope" (evidence D, p.172). We are struggling to understand how this study and the extension of aromatase inhibitors is out of scope of the question: "What is the optimal duration of adjuvant endocrine therapy for people with ER+ breast cancer?" and would urge the extension of Aromatase Inhibitors to be considered.	Thank you for your comment. The focus of the review question was to compare 5 years of endocrine therapy (which has been considered the standard) with greater than 5 years of therapy; therefore, the reference you mention was outside the scope of the protocol as the length of endocrine therapy in the comparison arm (which included both tamoxifen and aromatase inhibitors) was greater than 5 years and already considered extended therapy. There was insufficient evidence found to make a recommendation on the extension of endocrine therapy in women who had been taking an aromatase inhibitor for 5 years (as the only endocrine therapy received) as all of the included studies had 5 years of tamoxifen therapy as the comparison arm.
Breast Cancer Clinical Expert Group	Draft	11	2-3	Recommendation 1.7.4 should be clarified: Ovarian function suppression has not been shown to give additional benefit to tamoxifen in lower risk breast cancer not requiring chemotherapy.	Thank you for your comment. This clarification is provided in the following recommendation (1.7.5) which states that 'ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy'.

[6] Goss, 2016. **Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years.** New England Medical Journal 375:209-219. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1604700

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Breast Cancer Clinical Expert Group	Draft	14, 15	14-23 1-19	We welcome the recognition of the use of adjuvant bisphosphonates to improve outcomes. The differences in methodology in assessment of data from meta-analyses has led to a difference in the recommendation compared to the original EBCTG meta-analysis.[7] The assessment of 'high risk of recurrence' is varied but the clinical guidelines for bisphosphonates produced by the Sheffield group have suggested 12% risk of breast cancer death at 10yrs and have been in common usage since 2016.[8] We would suggest their reference.	Thank you for your comment. You are correct that differences in methodology meant that we were unable to include all the studies in the EBCTCG meta-analysis in our review; we also considered additional studies that were not included in the EBCTCG meta-analysis. The 12% risk suggested by the Sheffield group is based on level or risk estimated by Adjuvant online, which is no longer available. Therefore, the committee agreed it was not appropriate to use this reference.
Breast Cancer Clinical Expert Group	Draft	15, 16	22, 8	We welcome recommendations 1.10.1 and 1.10.2.	Thank you for your comment and support for these recommendations.
Breast Cancer Clinical Expert Group	Draft	16	15-17	We disagree with recommendation 1.10.4. Multicatheter interstitial brachytherapy should NOT be included in the guidelines. Follow up has not been long enough and there is a higher recurrence rate with this modality of radiotherapy.[9] There	Thank you for your comment. The recommendation to consider interstitial brachytherapy has been removed as the committee agreed that although it is effective it is unlikely to be acceptable to the majority of people.

[7] Early Breast Cancer Trialists' Collaborative Group, Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015; 386:1353-61.
[8] The Sheffield Group, 2016. Prescribing Guidance for Ibandronic Acid 50mg tablets in post-menopausal women with breast cancer. P.7. Available from: http://medicinesmanagement.doncasterccg.nhs.uk/wp-content/uploads/2016/12/Guideline-ibandronic-acid-in-breast-cancer-final.pdf
[9] Coles, 2015. Accelerated partial breast irradiation: the new standard? The Lancet Volume 387, No. 10015, p201–202. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00518-8/abstract

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				has been ongoing correspondence in the literature which is why we do not believe it is at all appropriate to be included.[10]	
Breast Cancer Clinical Expert Group	Draft	16, 17	26, 7	In recommendation 1.10.6 the statement that there is no increase in cardiac failure, myocardial infarction or secondary cancer if radiotherapy is given is incorrect. There is a small increase in cardiac morbidity in left sided tumours.[11] This is very significant in current smokers and lung cancer is also increased in this group.[12] These risks are currently listed in all patient consent forms. If this change in the Guidelines were accepted then the implication is that consent forms should also be rewritten to exclude them. Most clinicians would disagree with this.	Thank you for your comment. The lack of increase in cardiac failure, myocardial infarction or secondary cancer is in the specific group of very low risk women specified in the previous recommendation where we did not have any evidence of increased risk, and the wording of this recommendation has been amended so that this is clearer. It will therefore not be necessary to amend all consent forms, as these risks will need to be included for the majority of people. The references you mention were not included in the current review as they refer to a non-RCT (23) and a review of radiotherapy that is not compared against no radiotherapy (24). The recommendations to minimise the cardiac morbidity when treating left-sided tumours have been moved to the beginning of the radiotherapy section so it is more obvious that they refer to all the other recommendations in the radiotherapy section. The evidence for the additional impact of smoking on lung cancer was not included in this review so we were unable to make specific recommendations relating to the effects of smoking.

[10] Vratislav Strnad, 2016. Partial breast irradiation and the GEC-ESTRO trial: Author's response. The Lancet. Available from: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)00697-8.pdf
[11] Sarah Darby, 2013. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. New England Journal of medicine. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1209825
[12] Aznar et al, 2018. Exposure of the lungs in breast cancer radiotherapy: A systematic review of lung doses published 2010-2015. Radiotherapy Oncology Journal. Available from: http://www.thegreenjournal.com/article/S0167-8140(17)32742-1/fulltext

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Breast Cancer Clinical Expert Group	Draft	17	12-15	We strongly agree with recommendations 1.10.8 and 1.10.9.	Thank you for your comment. We welcome your support for these recommendations.
Breast Cancer Clinical Expert Group	Draft	17	17-19	There are data supporting post mastectomy for 3 or more node positive cancers, but it shows the benefit is smaller for 1-3 nodes.[13] In recommendation 1.10.10 the statement that they should be given to all node positive cancers may represent over treatment. This should be explained appropriately to the patients.	Thank you for your comment. The committee agree that this may represent over-treatment and that future data from the SUPREMO trial may help address this. However, subsequent recommendations do define the populations in more detail, and allow the option of not carrying out post-mastectomy radiotherapy in those with low risk. The evidence available to the committee, which included the EBCTCG meta-analysis you reference and four additional trials, did not allow a distinction to be made for the benefit of radiotherapy in people with 1 to 3 positive nodes, compared to those with 4+ positive nodes. Reduced loco-regional recurrence was seen in women with 1 to 3 positive nodes who were given radiotherapy, even when the tumour size was small (0 to 19 mm), and there was no difference in magnitude of this effect compared with medium or larger tumours. Furthermore, the magnitude of difference seen with radiotherapy in the evidence reviewed by the committee was not smaller for 1-3 nodes (14% difference in recurrence, RR=0.24) compared to 4+ nodes (11% difference in recurrence, RR=0.39)
Breast Cancer	Draft	21	1-3	We disagree with recommendation 1.11.10. The use of pre-treatment sentinel node data is highly controversial and is increasingly seen as inappropriate. It rules out the possibility of	Thank you for your comment. There was insufficient data to confidently exclude any group from treatment as there was evidence of reduced locoregional recurrence in

[13] EBCTCG (Early Breast Cancer Trialists' Collaborative Group), 2014. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. The Lancet. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2814%2960488-8/abstract

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Clinical Expert Group				achieving Pathological Complete Response in nodes and thus avoiding axillary resection with the consequent risk of lymphedema.	subgroups based on clinical (pre-treatment) node status and subsequent response rate was not known. Therefore, the committee adopted the strength of the recommendations for post-mastectomy radiotherapy in people who did not have neoadjuvant chemotherapy (which has a larger, more robust, evidence base). However, the order of the recommendations has been changed to prioritise the most serious groups (those with post-treatment histology still showing involvement).
Breast Cancer Clinical Expert Group	Draft	25	1	We believe that methods of breast reconstruction should be added to the recommendations for research. There is not good evidence for which is the best method of reconstruction, and in particular whether implant or autologous reconstruction gives better long term outcomes, or whether these are equivalent, or which is the more cost effective, a further question related to this is the effect of radiotherapy on each. We would therefore like to see this added as a research need.	Thank you for your comment. The review question for breast reconstruction was focused on whether the potential need for radiotherapy precludes immediate breast reconstruction, and we did not look for comparative evidence on different methods of breast reconstruction. The committee are therefore unable to make a research recommendation as a NICE research recommendation can only be made if evidence has been searched for and a gap in the evidence has been identified.
Breast Cancer Clinical Expert Group	Draft	48	12-13	We would like to see the evidence for the figure of "5% of breast cancers being due to inherited mutations in high risk genes such as BRCA1/2 and p53". The figure that is more regularly cited is 2-3% of breast cancers.	Thank you for your comment. This figure was taken from the NHS England publication, Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations (Reference: NHS England E01/P/b, 2015). A copy of the document can be found on the NHS England web site here: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-e/e01/
Breast Cancer Now	General	General		We welcome this update to the guideline on early and locally advanced breast cancer. Overall, the recommendations represent important steps in the right direction for people with early breast cancer. However, as it has been nine years since the guideline was last updated, we believe that in some cases the recommendations are playing 'catch up' with clinical practice. Whilst we recognise that - given the sheer number of guidelines	Thank you for your comment and support for this guideline update. We agree that there are limitations in the guideline process as each topic takes time to update. However, the NICE surveillance teams schedule regular checks for new evidence, which can bring forward an update. In addition, the technology appraisal programme at

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				NICE produces - updates need to be strictly scheduled, guidelines need to be as up to date as possible in order to remain relevant to clinicians, providers and commissioners.	NICE permits new treatments to be considered outside of the guideline update process.
Breast Cancer Now	General	General		The draft updated guideline recommends that the risks and benefits of a particular course of treatment or, in some cases, of having no further treatment, are discussed with patients - including in relation to breast and axilla surgery, adjuvant bisphosphonate therapy and radiotherapy. In order to help patients make these decisions with their clinicians they need to be provided with the right information and support. Breast Cancer Now has spoken with a number of patients about the sort of information and support they feel they need to help them make these decisions. The issue of risks and benefits can be complicated, patients will have different levels of understanding, and may well still be in shock from their diagnosis and unable to easily take the information in. Some patients will want to have all the available information and some will not, and so clinicians will need to tailor the information they provide to individual patients needs and preferences. It is important that patients are given time to digest the information they have been given as well as the opportunity to ask questions outside of appointments. We spoke to some patients that had received all, or most, of the information they felt they needed to help them make decisions with their clinicians about their treatment. However, others had received little or no information, and had to prompt clinicians to get information or do their own research. Many patients told us that they welcomed written information in addition to a discussion with their clinician (which was particularly important given that if	Thank you for your comment and for sending this feedback about giving information to people with breast cancer. We agree that it is important to provide timely, appropriate information tailored to the person involved, including details of the benefits and harms of courses of treatment. This is acknowledged at the start of the short guideline as follows: 'People have the right to be involved in discussions and make informed decisions about their care, as described in your care. https://www.nice.org.uk/about/nice-communities/public-involvement/your-care' This theme is then taken up in the recommendations which include factors to consider when providing information to each person. In order to help people make these decisions we have also included a number of preference sensitive decision point tables in the guideline which provide more details of the risks and benefits to be considered. In addition to this, further information for patients is provided on the 'Information for patients' tab on the guideline page of the NICE website, when the guideline is published.

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				they were still in shock from their diagnosis they may not be able to absorb all they were being told, or that some information may not feel important at the time but would prove to be useful later on) and also thought that they should be signposted to groups or organisations (including 'virtual' groups such as reputable online forums) that could provide further information or support if they felt they needed it.	
Breast Cancer Now	General	General	N/A	Breast Cancer Now welcomes the inclusion of a recommendation on providing advice on the lifestyle factors that can help to prevent the recurrence of breast cancer. Some patients that we spoke to had received such advice, but others had not. In some cases the treatment that patients are receiving can impact on their ability to implement this advice - for example hormone therapies can impact on people's weight and ability to exercise. Some patients may therefore need support to implement this advice, and as part of these discussions clinicians should provide details of any support that might be available (please also see comments 2 and 13 on this).	Thank you for your comment. We agree that the provision of lifestyle advice is an important new section of the guideline, and have included links to three other existing NICE guidelines which provide more specific advice on preventing excess weight gain, obesity and physical activity.
Breast Cancer Now	Draft	5	12-13	Breast Cancer Now supports the recommendation, originally made in the 2009 version of the guideline, that everyone with breast cancer should be offered prompt access to specialist psychological support, and where appropriate, psychiatric services. A diagnosis of breast cancer can come as a shock and have a huge emotional and psychological impact on patients and their loved ones, and this support can help ensure patients have a more positive experience of treatment and care. However, access to psychological support varies across the country.[14] Many	Thank you for your comment and support for the recommendation on psychological support. This section of the guideline was not included in the update, but has been amended to include a link to the NICE guidelines on patient experience in the NHS which provide additional information on making psychological support available where necessary.

[14] A Mixed Picture: An Inquiry into geographical Inequalities and Breast cancer, All-Party Parliamentary Breast Cancer, February 2018.

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				patients that we have spoken with were not told about such services. This is an area which NICE could helpfully concentrate on in the tools and resources it provides to help put the guideline into practice.	
Breast Cancer Now	Draft	5	9-10	Breast Cancer Now is very concerned that the requirement in the 2009 guideline for all patients with breast cancer to be assigned to a named breast cancer nurse specialist who will support them through diagnosis, treatment and follow up has been replaced with a requirement for them to have a named key worker to do this. We know from patients that access to a clinical nurse specialist (CNS) can have a positive impact on their experience of care. The Cancer Patient Experience survey shows, for example, that patients with a CNS are 48% more likely to be given written information about their cancer and 55% more likely to be told about the long term side effects of treatment.[15] However, there is variation by Clinical Commissioning Group (CCG) in the percentage of breast cancer patients both being given the name of a CNS (between 76% to 100%) and being able to contact them easily (58% to 100%).[16] Macmillan Cancer Support has been conducting a census of CNS's which will be used to inform the Heath Education England cancer workforce strategy. However, the increase in the number of people with breast cancer (and cancer more generally) is widely accepted to mean that CNS's have less time for each patient. Whilst key	Thank you for your comment. This recommendation has now been amended to state that people 'should have a named clinical nurse specialist or other specialist key worker with equivalent skills'. This reflects the fact that the committee recognised that people should have access to someone with the appropriate clinical knowledge and skills to support them, but that did not necessarily always have to be a nurse.

[15] National Cancer Patient Experience Survey, Quality Health, 2014. Cited in The C Word: How we react to cancer today, Macmillan Cancer Support, July 2017.
[16] National Cancer Patient Experience Survey 2016, Quality Health, CCG data tables.

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				workers may be able to assist with workload by dealing with administrative tasks, freeing up CNS's to spend more time with patients, they cannot and should not be considered an alternative to the clinical care provided by a nurse specialist.	
Breast Cancer Now	Draft	8	2-16	Breast Cancer Now welcomes the confirmation that women should be offered immediate reconstruction, including where they may need radiotherapy. Research presented at the recent UK Interdisciplinary Breast Cancer Symposium provided further evidence that immediate reconstruction does not delay the start of adjuvant therapy, including chemotherapy and radiotherapy, although it may increase the risk of complications requiring readmission.[17] Breast Cancer Now is aware that some CCGs have imposed restrictions on either the number of operations that women can have to reconstruct their breasts following a mastectomy, or the time period in which they can have them, or both. As the draft updated guideline identifies, immediate reconstruction can lead to cost savings. However, restrictions placed on services must always be based on evidence and what is in the best interests of the patient. It may be reasonable to restrict the number of surgeries a patient can have, as long as surgeries are planned sufficiently and there is good communication between a patient and their surgeon. However, a patient who does not achieve a satisfactory outcome	Thank you for your comment and for supporting the recommendations on immediate breast reconstruction. The committee agree that surgery should be planned and carried out to achieve aesthetic satisfaction for the person, and symmetry where required. Implementation of this guideline will require CCGs to commission services to achieve these goals. The committee also agreed that women may choose not to have reconstruction. We have amended the recommendations on breast reconstruction to clarify that some women may choose to have no breast reconstruction. The recommendations have also been amended with the inclusion of a preference sensitive decision point table, summarising the topics which may need to be included in a discussion of the risks and benefits of different methods of reconstruction.

[17] The research [resented was from the iBRA-2 study. Information on the research presented can be found here: http://breastcancernow.org/news-and-blogs/news/immediate-breast-reconstruction-after-mastectomy-does-not-delay-start-of-chemotherapy-or-radiotherapy-%E2%80%93-but-may-increase-risk-of-complications-and-readmission

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				in a set number of procedures should not be penalised and should be able to return for corrective surgery. Patients should be able to come to a decision on breast reconstruction in their own time and access to this surgery should never be restricted by time. The majority of women choose not to have reconstruction. However, whilst immediate reconstruction can offer benefits, many women may wish to delay breast reconstruction for a range of reasons. During discussions of the risks and benefits of breast reconstruction, clinicians should make clear that delaying reconstruction is an option, and this option should not be restricted to reduce costs.	
Breast Cancer Now	Draft	11	11-22	Breast Cancer Now welcomes the recommendations on extending adjuvant endocrine therapy. A recently published meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that breast cancer recurrences occurred at a steady rate from 5 to 20 years.[18] Of the patients we spoke to with hormone positive breast cancer some told us they had already had their hormone therapy treatment extended. However, hormone therapy can have unpleasant side effects that in some cases can cause patients to stop taking them before they have completed the full course. Some patients told us that the possible side effects had not been discussed with them when they started treatment. As the draft updated guideline identifies, taking hormone therapy for more than 5 years can increase the	Thank you for your comment. The committee agreed that the risks and benefits of extended endocrine therapy were important and a preference sensitive decision point table has been included at this point in the guideline to assist with the discussion of risks and benefits of extended endocrine therapy.

[18] Early Breast Cancer Trialists' Collaborative Group, 20 Year Risks of Breast Cancer Recurrence after stopping Endocrine Therapy at 5 Years, New England Journal of Medicine, 2017; 377:1836-1846.

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				risk of problems and patients need to be informed of the risks and benefits so they can make a choice about this. It is therefore not clear why a recommendation around discussing the risks and benefits of extended hormone therapy with patients has not been included, as it has done with other recommendations, such as those on bisphosphonates. As part of discussions on hormone therapy, patients should be given information on side effects, what they can do to help cope with them, and any support the hospital or other organisations or groups may provide, such as Cognitive Behavioural Therapy, to help reduce the impact of symptoms.	
Breast Cancer Now	Draft	11	11-22	The recommendations on extended endocrine therapy cover extended use of tamoxifen and switching from tamoxifen to an aromatase inhibitor. The guideline recommends tamoxifen as initial adjuvant endocrine therapy for premenopausal women and men with hormone positive breast cancer, postmenopausal women at low risk of recurrence, or where aromatase inhibitors are contraindicated or not tolerated. The guideline recommends aromatase inhibitors as initial adjuvant endocrine therapy for postmenopausal women at medium to high risk of recurrence. It would be helpful to understand why there is no such recommendation about extending aromatase inhibitor therapy.	Thank you for your comment. There was insufficient evidence found to make a recommendation on the extension of endocrine therapy in women who had been taking an aromatase inhibitor for 5 years.
Breast Cancer Now	Draft	14, 15	22-23, 1-3	Breast Cancer Now supports the recommendation that clinicians should discuss the risks and benefits of adjuvant bisphosphonate therapy with patients. The side effects of bisphosphonates are well known, and whilst some, such as ONJ, are very rare (trials suggest they occur in less than 1%) they are also very serious. There are a number of steps that can be taken to help prevent	Thank you for your comment. We agree that a discussion of the risks and benefits surrounding the use of bisphosphonates is important and this is included in recommendation 1.9.3. This recommendation also contains a link to the MHRA/CHM advice on

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				ONJ including having a dental check-up and completing any treatment before starting treatment and maintaining good oral health. Please also see comment 2 about discussion of risks and benefits with patients.	bisphosphonates which includes more detailed information about dental health, as you suggest.
Breast Cancer Now	Draft	14	16-21	Breast Cancer Now welcomes the recommendations on adjuvant bisphosphonates. We have been working to help ensure that adjuvant bisphosphonates are made routinely available to postmenopausal women to reduce the risk of breast cancer recurring and improving survival from breast cancer. The draft guideline recommends that adjuvant bisphosphonates are offered to postmenopausal women with node positive invasive breast cancer and considered for postmenopausal women at high risk of recurrence. No definition is given of 'high risk of recurrence' and it would be helpful if a broad definition could be encouraged. However, given the potential benefits to patients we would like to see the guideline recommend that adjuvant bisphosphonates are offered to a wider group of postmenopausal women. Our position is based on the important evidence provided by the Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis of all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. This showed significant reductions in the risk of recurrence, distant recurrence, bone recurrence and breast cancer mortality in postmenopausal women taking adjuvant bisphosphonates. The absolute reduction in risk at 10 years for bone recurrence was 2.2%, and breast cancer mortality was 3.3%. These absolute	Thank you for your comment and your offer to share data with NICE. There was stronger evidence of benefit in the node-positive and postmenopausal group so the recommendation is an offer recommendation for this group. However, the committee agreed that high risk is determined on an individual patient basis, depending on prognostic tools and factors such as the tumour type, size, grade and comorbidities and did not think a broad definition of high risk was possible in this instance; therefore a consider recommendation was made for other high-risk postmenopausal women. The committee did not feel that adjuvant bisphosphonates should be offered to a wider group of women as, for the lower risk women, the harms are likely to outweigh the benefits. You are correct that differences in methodology meant that we were unable to include all the studies in the EBCTCG meta-analysis in our review; however, we also considered additional studies that were not included in the EBCTCG meta-analysis. The role of NICE guidance is to evaluate the evidence and make recommendations based on that evidence, and not necessarily to fall in line with other pre-existing guidelines.

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				reductions showed no significant difference in benefit as a result of factors such as hormone receptor status, lymph node involvement or tumour grade.[19] We recognise that the meta-analysis was not included in the evidence review that NICE conducted on this issue because some of the trials it covered were not consistent with the protocol for the review, although some of the trials covered by the meta-analysis were included in the review in their own right. However, the meta-analysis has been used as the basis for clinical guidelines on adjuvant bisphosphonates in North America and Europe as well as clinical advice from the Clinical Expert Group (CEG) for Breast Cancer convened by NHS England as part of the national cancer programme - all of which recommend that adjuvant bisphosphonates are offered to a wider group of postmenopausal women.[20] [21] [22] This leaves the draft NICE guideline out of step with other key clinical guidance on this issue. Breast Cancer Now has undertaken work to estimate the patient populations for different groups of women that could be offered a bisphosphonate and the number of deaths that could be prevented per annual cohort of patients in England, which we would be happy to share with NICE.	

[19] Early Breast Cancer Trialists' Collaborative Group (2015), Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015; 386:1353-61.
[20] Dhesy-Thins, S et al, Use of Adjuvant Bisphosphonates and Other Bone -Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline, J Clin Oncol 35;2062-2081.
[21] Hadji P et al, Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel, Annals of Oncology 27, 3: 379-390.
[22] Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services, Breast Cancer Clinical Expert Group, August 2017.

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Breast Cancer Now	Draft	14	16, 19	We note that the bisphosphonates recommended are zoledronic acid, which is delivered intravenously) or sodium clodronate (which is taken orally). The CEG clinical advice recommends zoledronic acid and ibandronate, although both the North American and European guidelines recommend zoledronic acid and sodium clordronate. Whilst we recognise that zoledronic acid and sodium clodronate may have been trialled in greater numbers of participants, the EBCTCG meta-analysis showed no difference in efficacy between zoledronic acid, sodium clodronate and ibandronate. Early data presented at the American Society of Clinical Oncology conference in 2015, which compared the efficacy of zoledronic acid, sodium clodronate and ibandronate, indicates that disease free survival and overall survival did not differ between these bisphosphonates.[23] Whilst we recognise that an abstract cannot be included in NICE's evidence review, when the full results of this trial have been published and considered NICE must quickly update the clinical guideline to reflect them. There is a significant difference between the cost of sodium clodronate compared to ibandronate and zoledronic acid.[24] Given	Thank you for your comment. There was insufficient evidence of benefit for bisphosphonates other than sodium clodronate or zolendronic acid in the evidence reviewed by the committee. However, we appreciate that new evidence is being published all the time and will inform surveillance of the study you mentioned for consideration in a future update. The committee were aware of the differing costs of the bisphosphonates but chose to recommend the bisphosphonates with the strongest clinical evidence base. Furthermore, the economic analysis showed that in scenarios where bisphosphonates were assumed to be effective, they were also likely to be cost-effective and this applied even when considering the higher cost associated with sodium clodronate. Thank you for the information on funding patterns by CCGs. Commissioning decisions should take NICE guidance into consideration.

[23] Gralow, J et al (2015) Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials group/NRG Oncology study S0307 in 2015 ASCO Annual Meeting, Journal of Clinical Oncology 33.

[24] The drug tariff lists the price of a pack of 60 800mg tablets of sodium clodronate as £146.43 (the standard dose for cancer indications is 1600mg per day meaning the cost of a years' worth of treatment would be £1781), and a pack of 28 50mg tablets of ibandronate as £5.83 (the standard dose for cancer indications is 50mg per day meaning the cost of a years' worth of treatment would be £76). The drugs and pharmaceutical electronic market information tool lists the average price paid by Trusts for

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				the well-documented financial pressures in the NHS, we are concerned that, moving forward, more CCGs may decide to fund only zoledronic acid as a result of this recommendation. This could restrict the ability of clinicians to prescribe the bisphosphonate that best suited patients in terms of their likely sensitivity to the different side effects of particular bisphosphonates, and their ability and willingness to visit hospital for treatment. Breast Cancer Now sent FOI requests to all CCGs in 2017 asking whether they were routinely funding bisphosphonates for this indication, and if so, which bisphosphonates they were funding. At that time 42 CCGs were routinely funding bisphosphonates for this indication, and of those which provided information about which bisphosphonates they were funding, only two told us they were funding sodium clodronate - and in both cases zoledronic acid and ibandronate were also being funded. Eleven told us they were only funding zoledronic acid. Breast Cancer Now has undertaken financial modelling work for the various potential patient populations and bisphosphonates which looks at the overall costs and savings that could be made in a variety of scenarios, which we would be happy to share with NICE.	

4mg/100ml of zoledronic acid as around £5, which at a dose of 4mg/100ml every 6 months would mean the cost of a years' treatment would be £15 in the first year and £10 in subsequent years.

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Breast Cancer Now	Draft	14	16,19	The draft updated guideline does not make any recommendations about the dosage or duration of treatment with adjuvant bisphosphonates. The North American and European clinical guidelines both recommend 1600mg of sodium clodronate daily (the standard dose for cancer indications) and 4mg per 100ml of zoledronic acid every 6 months. Although the doses of zoledronic acid used in clinical trials have varied, the EBCTCG meta-analysis showed no difference in benefit between high and low intensity schedules of zoledronic acid for bone recurrence, and low intensity schedules may reduce the risk of the serious side effects associated with intravenous bisphosphonates such as osteonecrosis of the jaw (ONJ). The duration of treatment for oral bisphosphonates sodium clodronate and ibandronate in clinical trials was generally 2 -3 years. There was wider variation in the duration of treatment with zoledronic acid. The EBCTCG meta-analysis showed no difference in benefit between shorter and longer treatment durations for bone recurrence. In order to mitigate the risk of serious side effects such as ONJ which are particularly associated with intravenous bisphosphonates a shorter treatment duration may therefore be preferable. Treatment duration of 3 years for both oral and intravenous bisphosphonates would be in line with the recommendations of the North American and European guidelines and CEG clinical advice.	Thank you for your comment. The evidence review looked at which groups of people would benefit from the use of adjuvant bisphosphonates and did not look at the dosage or duration of treatment so the committee were unable to make any specific recommendations on this.
Breast Cancer Now	Draft	14	16, 19	The draft updated guideline should clarify that the term 'postmenopausal' covers premenopausal women receiving	Thank you for your comment. The committee did not look at evidence for the sub-group of people on ovarian function

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				ovarian suppression therapy as part of their treatment for breast cancer. The North American and European guidelines and the CEG clinical advice all recommend that these women should covered. The ABCSG-12 trial in pre-menopausal women having ovarian suppression therapy demonstrated improvements in disease free survival and overall survival.[25]	suppression (OFS), so were unable to make any specific recommendations for this group. However, the recommendations as they stand do not exclude people on OFS. The use of bisphosphonates in natural menopause versus treatment-related menopause was not included in the evidence review for adjuvant bisphosphonates so the committee were also unable to make any recommendations on this.
Breast Cancer Now	Draft	24	12	Clinical follow-up after active treatment is hugely important. Even patients that had a good experience with their treatment told us that this was where things often 'fell down' and that they felt they did not have enough information about what would happen next, or that their experience did not match what they were told would happen. Patients with particularly aggressive breast cancers, such as triple negative breast cancer, have emphasised how important better follow-up and management is. In some areas services to support patients are being implemented, such as the 'recovery package' in Greater Manchester which includes holistic needs assessment and care planning at significant points in the patient pathway, treatment summaries after significant phases of treatment, cancer care review in primary care and health and wellbeing events to provide information and support.[26] Charities such as Breast Cancer Care have developed courses for patients finishing treatment to give them information and advice to help manage their condition and	Thank you for your comment. The proposal not to include the clinical follow-up section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.

[25] Gnant, M et al (2015), Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozole plus ovarian function suppression in premenopausal early breast cancer: final analysis of the USTRIAN Breast NCA colorectal Cancer Study Group Trial 12, Annals of Oncology, 26 (1), 313-320.
[26] A Mixed Picture: An Inquiry into geographical Inequalities and Breast cancer, All-Party Parliamentary Breast Cancer, February 2018.

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				make healthy lifestyle choices (please also see comment 14 on this) - however provision is patchy as we understand that some nursing teams do not have the resources to take part.[27] As part of clinical follow-up, the draft updated guideline recommends that patients should be provided with information on the signs and symptoms to look out for. This should specifically include the signs and symptoms of secondary, or metastatic, breast cancer. Research suggest that less than a quarter of women (22%) with secondary breast cancer knew what to look for.[28] Clinical follow-up is an area which NICE could helpfully concentrate on in the tools and resources it provides to help put the guideline into practice.	
Bristol Myers Squibb	General	N/A	N/A	Thank you for the opportunity to comment on this guideline. At this moment in time, we have no comments on the draft guideline. Many thanks,	Thank you for your response and for confirming that you have not comments to make at this time.
British Association of Surgical Oncology (BASO)	Draft	General	General	This document is not sufficiently robust and needs further work. As it stands, it is less robust than the 2009 guidelines and less robust than other international guidelines – eg: the German guidelines. Each recommendation should be annotated with the level of evidence supporting it, along with the list of references.	Thank you for your comment and feedback about the NICE guideline process. NICE does not annotate recommendations (as outlined in the methods manual), rather we use 'offer' and 'consider' to reflect strength of a recommendation. The short guideline now includes

[27] Ibid.
[28] Secondary breast cancer, Part one: diagnosis, Breast Cancer Care, July 2016.

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				The rationale section should provide scientific reasons for accepting or rejecting comments received during public consultation.	rationale and impact sections so that readers can quickly find the reasoning behind recommendations. These sections then refer to the full evidence reports, which include summaries of the evidence, the GRADE tables (in which the quality of the evidence is rated by outcome and used to inform the strength of the recommendations), full reference lists and committee discussions: these are amended following the receipt of stakeholder comments as necessary. The responses to comments received during the public consultation are published on the NICE website, and this includes the scientific reasons for accepting or rejecting comments.
British Association of Surgical Oncology (BASO)	Draft	4	12,13	Breast MRI is not necessary for all lobular cancers. Replace with:' to assess the tumour size if breast-conserving surgery is being considered for invasive lobular cancer and the level of mammographic density precludes accurate assessment of disease extent'	Thank you for your comment. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.
British Association of Surgical Oncology (BASO)	Draft	5	2,3,4	We are concerned that routine axillary ultrasound may encourage excessive axillary biopsy and increase the rate of axillary clearance. Routine axillary ultrasound was not recommended in any of the 7 randomised controlled trials comparing sentinel node biopsy to axillary clearance. It was also not recommended in Z011. Recommend changing to: 'Perform pretreatment ultrasound evaluation of the axilla for people having investigations for early invasive breast cancer and document findings. Routine biopsy of axillary nodes is not recommended for normal or indeterminate axillary nodes. Only if abnormal lymph nodes are identified, perform ultrasound-guided needle sampling.'	Thank you for your comment. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest or include the references that you have highlighted. However, we will inform the surveillance team of this evidence for consideration in the next update.

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British Association of Surgical Oncology (BASO)	Draft	6	6	Units should be auditing their local recurrence rates with DCIS and with invasive breast cancer.	Thank you for your comment. The committee agreed that recurrence rates after surgery for all types of early and locally advanced breast cancer should be audited, and have amended the recommendation so it is no longer specific to DCIS.
British Association of Surgical Oncology (BASO)	Draft	7	8-10	This contradicts the next section (lines 11,12,13). Also, the recommendation for radiotherapy is based on the AMAROS trial. This trial only included patients with low burden axillary disease at sentinel node biopsy (similar to the Z011 patients) and no control arm. Therefore, it is likely that many of these patients would benefit from no axillary treatment rather than axillary radiotherapy instead of no treatment – we just don't know. Therefore, the safest interpretation of the data is to recommend surgery in those patients where further treatment is deemed necessary (high burden axillary disease). Change to 'Offer further completion clearance surgery after SLNB to people who have 2 or more sentinel lymph node involved with macrometastases. Consider axillary radiotherapy as an alternative in patients with co-morbidity.'	Thank you for your comment. The populations considered in 1.4.7 and 1.4.8 are different and therefore the recommendations do not contradict each other. There was evidence in support of axillary treatment for those with pathologically proven involvement of axillary sentinel lymph nodes, the population referred to in 1.4.7 ('people who have 1 or more sentinel lymph node macrometastases') which allowed the committee to make an offer recommendation. But there were unclear benefits and risks of further axillary treatment for the subgroup referred in 1.4.8 with 1 or 2 sentinel lymph nodes who had also been advised to have whole breast radiotherapy and systemic therapy. While the subgroup in 1.4.8 would also be offered further axillary treatment the risks and benefits of no further axillary treatment should also be discussed as an option (ideally as part of a clinical trial). The choice of axillary treatment depends on patient preference, comorbidities and the potential benefits and risks. The evidence showed there was no significant difference between surgery or radiotherapy so that is why both these have been included as options.
British Association of Surgical Oncology (BASO)	Draft	7	11-13	The section in brackets contradicts this statement. Recommend removing '(within clinical trials where applicable)'	Thank you for your comment. The committee wished to encourage recruitment into ongoing clinical trials in this area and so the statement in brackets has been left in place.

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British Association of Surgical Oncology (BASO)	Draft	8	2-5	There is insufficient level 1 evidence for this recommendation. Change to 'Discuss immediate breast reconstruction with women who have been advised to have a mastectomy, including those who may need radiotherapy, unless they have significant comorbidities that rule out reconstructive surgery.'	Thank you for your comment. The committee were aware that randomised controlled trials were not available for this review but the recommendations were based on more than 20 cohort studies. The committee agreed that radiotherapy did not lead to harms after immediate or delayed reconstruction or to a delay to adjuvant therapy following immediate reconstruction and therefore immediate reconstruction is a viable option. The recommendations on breast reconstruction have been amended to make it clear that both delayed and immediate reconstruction are viable options and both should be offered. To help discussions on the risks and benefits of both options, a preference sensitive decision point table has also been included, outlining some of the topics which should be included in the discussion and decision-making process.
British Association of Surgical Oncology (BASO)	Draft	15	21-23	We are concerned that need for radiotherapy is not considered at the outset, precluding the option of considering partial breast radiotherapy technique including intra-operative radiotherapy. Add initial point:' Consider need for adjuvant radiotherapy in all patients considered for breast conserving surgery at the initial pre-operative multidisciplinary discussion, and consider indication for intra-operative and partial breast radiotherapy as alternatives to external beam radiotherapy. '	Thank you for your comment. The population of people covered by this recommendation (people receiving radiotherapy after surgery who have clear margins) are different from the population who receive intra-operative radiotherapy where the margin status is unknown. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.
British Association of Surgical Oncology (BASO)	Draft	16	1-8	We are concerned that this section contradicts the recent NICE recommendation to offer selected patients Intrabeam intraoperative radiotherapy at sites with the equipment (31st January 2018, TA501). We suggest changing this section to: 'Consider intra-operative or partial breast radiotherapy (as alternatives to whole breast radiotherapy) for women who have	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.

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				had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who ….'	
British Association of Surgical Oncology (BASO)	Draft	16	18-25	Omitting radiotherapy (and using endocrine therapy only) increases local recurrence rate (compared with whole breast or partial breast radiotherapy), even in the most selected series. The increase might be small or 'acceptable' but this should be communicated to patients some of whom may chose intra-operative radiotherapy or another partial breast radiotherapy technique. Encouraging patients over the age of 65 to have no radiotherapy and not offering them an alternative, could also be perceived as 'ageist'	Thank you for your comment. The higher recurrence rates seen when omitting radiotherapy are detailed in the recommendations and should form part of the discussion when considering if radiotherapy can be omitted for individual people. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline. People aged over 65 are offered endocrine therapy as an alternative, and as this is a consider recommendation, the choice to omit or to receive radiotherapy would be made after an individualized discussion of the risks and benefits.
British Association of Surgical Oncology (BASO)	Draft	16	15-17	We are concerned that this section prevents patients choice by omitting intra-operative radiotherapy. Also multicatheter radiotherapy (requiring wires in the breast for 5 days) is not used in the UK and there is no cost effective or cosmetic outcome data supporting its use – we would recommend omitting this option. Change to: 'When offering partial breast radiotherapy, consider: • Intraoperative radiotherapy with Intrabeam (at sites with Intrabeam equipment) • external beam radiotherapy to a dose of 40 Gy in 15 fractions or 16'	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy, as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline. The recommendation to consider interstitial brachytherapy has been removed as the committee agreed that although it is effective it is unlikely to be acceptable to the majority of people.
British Association of Surgical Oncology (BASO)	Draft	17	1-4	The normal way to express risks in oncology is by considering the effect over time – typically at 5 years and 10 years- not annually. Presenting it per annum, is misleading. Change to: "Without radiotherapy, local recurrence occurs in about 50 per 1000 women at 5 years, and with radiotherapy, 10 women per 1000 at 5 years follow up.'	Thank you for your comment. The figures have been changed to cumulative values for 5 years as you have suggested.

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British Association of Surgical Oncology (BASO)	Draft	17	5-7	This is blatantly wrong – the opposite is true (eg: pulmonary fibrosis and angiosarcoma). This statement should be omitted.	Thank you for your comment. The lack of increase in cardiac failure, myocardial infarction or secondary cancer is in the specific group of very low risk women specified in the previous recommendation where there was no evidence of increased risk, and the wording of this recommendation has been amended so that this is clearer. The recommendations to minimise the cardiac morbidity when treating left-sided tumours have been moved to the beginning of the radiotherapy section so it is more obvious that they refer to all the other recommendations in the radiotherapy section.
British Association of Surgical Oncology (BASO)	Draft	18	9	1.10.14 Add discuss participation in the HTA, NIHR funded TARGIT-B trial, comparing intraoperative tumour bed boost to external beam radiotherapy boost, with suitable patients who meet the inclusion criteria. Or add this further down in the guidance where radiotherapy trials are discussed – highlighting it is open for recruitment.	Thank you for your comment. The proposal not to include the breast boost following breast-conserving surgery section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update only minor wording changes to the recommendation can be made and we are not able to make changes that alter the meaning.. However, that there is a new recommendation on supporting entry into clinical trials for people with breast cancer.
British Association of Surgical Oncology (BASO)	Draft	19	10-18	We are concerned this recommendation contradicts the latest published evidence namely EBCTCG meta-analysis demonstrating neoadjuvant chemotherapy is associated with a 5% increase in local recurrence at 15 year (Lancet Oncology January 2018) and the APHINITY Trial (NEJM, July 2017) demonstrating that dual anti-HER2 blockade confers no survival advantage and has only a very minor effect on local recurrence (7.1 vs 8.7%). In light of the later, the benefit of pertuzumab observed in smaller neoadjuvant trials (related to NICE TA424) should be limited to patients who require neoadjuvant chemotherapy for down-sizing to avoid mastectomy, and not to all	Thank you for your comment. The evidence reviewed by the committee showed that while there was an increase in local recurrence (from 9 to 12% for those that had neoadjuvant chemotherapy), the difference was not statistically significant; and there was no survival benefit, but this was not expected. There was benefit of reducing tumour size (11-83% response rate and 4-23% complete response) and a 15% difference in breast conservation rate with neoadjuvant chemotherapy. The EBCTCG meta-analysis was not included in our review as it was published after the cut-off date for our search; the APHINITY trial did

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				HER2 positive patients. Also, in men with breast cancer, there is no advantage with neoadjuvant chemotherapy (with the exception of inoperable cases). The whole section on neoadjuvant treatment provides no recommendation / indication on which patients should be considered for breast conserving surgery or how to present them with the advice that this increases local relapse at 15 years. This section should be replaced with: '1.11.1 Offer neoadjuvant chemotherapy to women with ER-negative invasive breast cancer as an option to reduce tumour size, if they have unifocal disease and wish to avoid mastectomy or to increase operability. [2018] 1.11.2 Offer neoadjuvant chemotherapy to women with HER2-positive invasive breast cancer in line with the NICE technology appraisal on pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer, if they have unifocal disease and wish to avoid mastectomy or to increase operability. [2018] 1.11.3 Consider neoadjuvant primary endocrine treatment or chemotherapy for women with ER-positive invasive breast cancer as an option to reduce tumour size if they have unifocal disease and wish to avoid mastectomy and to increase operability. [[2018]	not compare neoadjuavnt chemotherapy with no neoadjuvant chemotherapy and therefore was not included. The recommendations do not just apply to people with unifocal disease and the committee agreed it was more appropriate to say 'offer neoadjuvant chemotherapy... to reduce tumour size' as it may not be possible to avoid mastectomy or increase operability.
British Association of Surgical Oncology (BASO)	Draft	20	4-14	Primary endocrine therapy and its effects, are not supported by level 1 evidence. Women should be advised of the lack of level 1 evidence when considering primary endocrine treatment for down-sizing or for post-posing surgery.	Thank you for your comment. The committee reviewed level 1 evidence that showed neoadjuvant endocrine therapy is as effective as neoadjuvant chemotherapy (which has a greater evidence base) at reducing tumour size in postmenopausal women, and so were able to recommend its use in this specific group, but made an additional recommendation to ensure that the risks and

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					benefits for individual women were considered and discussed.
British Association of Surgical Oncology (BASO)	Draft	22	24	Replace with: ' Stop systemic hormone replacement therapy (HRT) in women who are diagnosed with breast cancer or consider an alternative strategy including replacing it with a non-hormonal alternative.'	Thank you for your comment. The proposal not to include the menopause symptoms section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.
British Nuclear Medicine Society	Evidence Report B	General	General	Evidence Report B: Concerning sentinel node localization does NICE have a view concerning pre-operative gamma camera imaging in accurate localisation of the sentinel node	Thank you for your comment. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update no evidence concerning the use of pre-operative gamma camera imaging was reviewed.
British Nuclear Medicine Society	Evidence Report G	General	General	Evidence Report G: What is the view of NICE on the use of bone densitometry (DEXA), should this be done? When should it be done and how often?	Thank you for your comment. The bone health section of the guideline was not prioritised for this guideline update and so the use of DEXA was not examined and is not included in the evidence report. However, the short guideline contains recommendations from the previous NICE guideline on early breast cancer (CG80) which outlines which groups should have DEXA scans, and the algorithms referred to in recommendation 1.9.6 cover when DEXA scans should be repeated
Carl Zeiss Meditec	Draft	16	15-17	We are concerned that this recommendation may imply that the recent NICE guidance on Intrabeam (31 January 2018, regarding APBI treatment) is not considered. According to the NICE guidance, the possible treatment option with Intrabeam IORT for patients with early breast cancers should be considered in NHS centres where Intrabeam is available. Patients should be referred to the hospitals that have the Intrabeam equipment and the decision aid form from NICE should be used accordingly. Further	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy, as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.

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				remark: APBI with Intrabeam IORT is a cost-efficient APBI method, in Germany IORT is included into the S3 guideline for APBI as an equal modality to brachytherapy and external APBI.	
Department of Health	General	N/A	N/A	Thank you for the opportunity to comment on the draft for the above clinical guideline. . **I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation.** Many thanks and best wishes	Thank you for your response and for confirming that the Department of Health and Social Care has no substantive comments to make in this consultation.
Flat Friends UK	Draft	8	1	We are concerned that this recommendation may imply that reconstruction is the only option when faced with having mastectomy, when in fact, there are other options that are equally valid. In line with your recommendations on page 4 and your document "Your Care", you quote that "Your health care professionals need to know what matters to YOU – no two people are the same and they should listen carefully to your views and concerns" By offering immediate reconstruction to all patients unless they have significant comorbidities, is not, in our view, giving all options for symmetry that are available. Flat Friends UK is a registered charity who support ladies who are faced with, or have had a mastectomy and not had reconstruction. There are many ladies who do not want reconstruction and indeed want to have their remaining breast removed for symmetry. This surgery is being refused by their medical team and yet it is a valid option for symmetry for those ladies not wishing to have reconstruction. A second mastectomy would lower rates of complications and also the need for further complicated surgery, therefore saving on costs as well. The option of living without breasts should be discussed with all patients facing mastectomy, along with the	Thank you for your comment. We have amended the recommendations on breast reconstruction to include a separate recommendation stating that no breast reconstruction may be the preferred option for some women. The committee did not specifically consider the evidence for second mastectomy procedures, but we have added wording to the rationale and impact discussion about the importance of symmetry, so second mastectomy should be discussed as part of a consideration of breast reconstruction options to allow for symmetry. We agree that a full discussion about the risks and benefits of different breast reconstruction options should be held before surgery, and to help this discussion we have amended the guideline to include a preference sensitive decision point table summarising some of the considerations that should be included in this discussion.

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				reconstruction options, so that the patient is able to make a balanced and informed choice on which surgery is best for them. As you state in "Your Care" it is the patients right to be involved in making choices about their care and that must include surgical options as well. Our charity has nearly 2000 members and followers and we have great experience in supporting ladies in all issues surrounding living without reconstruction. We are happy to share our expertise and experiences to the NICE shared learning database. Contact trustees@flatfriends.org.uk	
Flat Friends UK	Draft	8	2-5	1.5.1 I would like to suggest that when discussing reconstruction prior to mastectomy, that the option of remaining 'flat' is also part of the conversation. It is not always the case that women want a reconstructed breast, but if they are not given the option, then many will think it's not something they could ask for. It should also be part of the process to offer those who feel that being flat is best for them, the opportunity to have a prophylactic mastectomy where a single mastectomy is required because of a cancer diagnosis. Reconstruction should include the option of having a fully flat chest with no extra skin left, in order that as smooth a surface as is possible is achieved. This option not only gives a good symmetry, but would also be cost effective, as a prophylactic mastectomy would obviously be less expensive than the often multiple surgeries required for a reconstructed breast, and often breast lift on the remaining breast. Women should be given all the choices available to them at the time. We should not have to fight for what we want. Some women will not ask the question. It should be offered, as a matter of course, alongside reconstruction.	Thank you for your comment. We have amended the recommendations on breast reconstruction to include a separate recommendation stating that no breast reconstruction may be the preferred option for some women. The committee did not specifically consider the evidence for second mastectomy procedures, but we have added wording to the rationale and impact discussion about the importance of symmetry, so second mastectomy should be discussed as part of a consideration of breast reconstruction options to allow for symmetry. We agree that a full discussion about the risks and benefits of different breast reconstruction options should be held before surgery, and to help this discussion we have amended the guideline to include a preference sensitive decision point table summarising some of the considerations that should be included in this discussion.
Genomic Health UK Ltd.	Draft	9	19	Recommendation 1.6.8 is misleading and would not support appropriately informing patients of their adjuvant treatment planning options. PREDICT cannot reliably predict whether an	Thank you for your comment. We agree that PREDICT alone is not a suitable tool for assessing the need for chemotherapy, and the recommendations include the use

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				individual patient will benefit from adjuvant chemotherapy (aCT). PREDICT and other solely prognostic tools can only attempt to identify patients estimated to have a sufficiently good prognosis that aCT would not be expected to provide a further meaningful absolute benefit to outweigh toxicity side-effects. It is important to be clear that PREDICT results are not directly actionable with regards to aCT treatment decision-making for the majority of patients. Patients found to have a moderate to poorer prognosis according to PREDICT can only be said to have the POTENTIAL to benefit from aCT. A large proportion of these patients will not actually benefit from chemotherapy (Oxford Overview reported that only ~10% of patients benefit). PREDICT website disclaimer: "PREDICT can only provide a general guide to possible outcomes in any individual case". PREDICT is also based on broad population trends in clinical-pathological features, limiting its reliable precision for individual patients.	of other predictive factors and consideration of the possible risks and benefits of treatment (recommendation 1.6.7). However, PREDICT does estimate benefits from adjuvant therapy and separates the estimated benefit of endocrine therapy and chemotherapy.
Genomic Health UK Ltd.	Draft	9	19	The UK Breast Cancer Group's (UKBCG) recent response to the NICE DG10 DCD consultation includes the statement *"We have had access to prognostic tools for many years, namely 'Adjuvant! Online' in the past and currently 'PREDICT'. However, prior to genomic tests clinicians clearly struggled to recommend no chemotherapy in 'intermediate' risk patients"*. This highlights the need to more precisely describe the suitable application and limitations of prognostic algorithm tools based on clinical-pathological features, such as PREDICT, in the updated CG80 guidance.	Thank you for your comment. The application of PREDICT is one of the tools to be used to assess the need for chemotherapy, as well as the use of other predictive factors and consideration of the possible risks and benefits of treatment (recommendation 1.6.7). Recommendation 1.6.9 which describes the limitations of PREDICT has been amended to make this clearer.
Genomic Health UK Ltd.	Draft	9	19	The above mentioned UKBCG's comment also highlights the need for gene expression profiling testing to be reflected in the CG80 guidance. Gene expression profiling testing, such as the Oncotype DX Breast Recurrence Score® assay, can further refine prognosis based on an individual's underlying tumour biology, to	Thank you for your comment. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE

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				more precisely identify patients with a very good prognosis, who can be safely spared aCT. Critically, some assays can also identify which individuals with a refined moderate-to-poor prognosis are likely to be sensitive to aCT treatment. To date, only the Oncotype DX Breast Recurrence Score® assay has been validated to discriminate between patient groups who derive a different relative risk reduction of distant recurrence from aCT i.e. can predict chemo-sensitivity. Therefore, this is the only test with directly actionable results for all tested patients, including those found to have refined moderate-to-poorer prognosis.	guideline on tumour profiling test to guide adjuvant therapy decisions [Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10)].
Genomic Health UK Ltd.	Draft	9	19	Suggested alternative wording for recommendation 1.6.8 (to reflect existing NICE guidance, including DG10): *"Use a standardized prognostic tool based on population trends of clinical-pathological features, such as PREDICT, to estimate prognosis to help guide adjuvant endocrine therapy and chemotherapy planning and to identify patients for gene expression profiling to further guide adjuvant chemotherapy planning (see section 'Adjuvant chemotherapy for invasive breast cancer' below)"*	Thank you for your comment. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on tumour profiling test to guide adjuvant therapy decisions [Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10)].
Genomic Health UK Ltd.	Draft	10	19	Footnote #4 *"Risk can be estimated using a range of standardised tools and clinical expertise"* partly contradicts recommendation 1.6.8, which implies that only PREDICT is / should be used. The same footnote has also been included in other areas of the draft recommendations. Available NHS evidence[1], as well as anecdotal information from the oncology community, indicates that other prognostic algorithm tools are used within the NHS today. Given this and the absence of a comparative NICE assessment of available prognostic tools, we would suggest that the availability of multiple tools should be reflected in recommendation 1.6.8 (see suggested alternative	Thank you for your comment. Standardised tools includes the use of PREDICT, but there are other tools that clinicians may wish to use in addition to this. A comparative assessment of the tools was carried out as part of the development of this guideline, which led to the recommendation to use PREDICT. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on tumour profiling test to guide adjuvant

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				wording for this recommendation above) [1]NHS Audit of Oncotype DX Breast Recurrence Score Use and Impact, as used to inform on-going DG10 assessment	therapy decisions, [Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10)].
Genomic Health UK Ltd.	Draft	12	11	It is highly surprising and irregular that the section 'Adjuvant chemotherapy for invasive breast cancer', makes no reference at all to the use of gene expression profiling for guiding adjuvant chemotherapy decisions (NICE DG10 guidance). This is an important advancement in breast cancer care. Indeed, NICE considered adoption of the DG10 recommendation a sufficiently high priority to create a Quality Statement specifically for this topic as part of the NICE Breast Cancer Quality Standards. To address this oversight, at the very least the DG10 recommendations should be summarized and clearly referenced in this section of CG80. A footnote would not be sufficient to reflect the importance of this topic. On page 4 of the CG80 draft recommendations, NICE states that *"People have the right to be involved in discussions and make informed decisions about their care, as described in your care"*. In line with this commendable objective, it is therefore important not to exclude existing NICE guidance which supports patient access to personalized biological information which can help them to make life-changing cancer treatment decisions.	Thank you for your comment. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10).
Genomic Health UK Ltd.	Draft	12	11	Recommendation 1.8.1 is flawed and would represent a significant backwards step in the care of early breast cancer in this country and should be revised. Whilst it is widely accepted that patients with a sufficiently good prognosis can be safely spared aCT, the current draft recommendation incorrectly implies that chemotherapy is 'indicated' for all remaining patients based on their prognosis alone. This is an alarming recommendation, particularly given that certain early breast cancer patients already	Thank you for your comment. Recommendation 1.8.1 offers taxanes to people where chemotherapy is indicated, and so would not necessarily increase the number of people receiving adjuvant chemotherapy in total. There was not enough evidence to specifically list sub-groups of people who could be safely excluded from receiving taxanes, but the recommendation in 1.8.1 to offer taxanes in addition to anthracyclines will not necessarily result in

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				have access (based on the NICE DG10 guidance) to their individual genomic information which is able to inform with far greater precision their likelihood of benefiting from aCT treatment. The current draft recommendation would lead to significant overall increases in aCT, leading to substantial overtreatment, as the Oxford Overview reported that only ~10% of EBC patients benefit from aCT. Many patients would receive aCT treatment who would not benefit but would needlessly experience debilitating side-effects with the associated negative quality of life impact, as well as placing considerable burden on already stretched NHS resources.	over-treatment as the decision will still depend on the an assessment of the benefits and risks in individual patients, which are described in 1.8.2. . In addition to the factors listed in 1.8.2 we have included a preference sensitive decision point table to help people and clinicians make a decision about the use of taxanes. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10).
Genomic Health UK Ltd.	Draft	12	11	We would like to suggest the following alternative recommendation to replace the current draft recommendation 1.8.1: *"For people with breast cancer of sufficient estimated risk[1], according to a standardized prognostic tool[2], that chemotherapy has the potential to provide a meaningful benefit:* • *gene expression profiling testing is recommended as an option for guiding adjuvant chemotherapy decisions for some patients (refer to NICE DG10)* • *for people for whom chemotherapy is indicated or judged to be advisable[3], offer a regimen that contains …etc"* [1] Risk of distant recurrence or mortality	Thank you for your comment and for your suggested rewording. The decision to offer a taxane will still depend on the assessment of the benefits and risks in individual patients, which are described in 1.8.2. In addition to the factors listed in 1.8.2 we have included a preference sensitive decision point table to help people and clinicians make a decision about the use of taxanes. Consideration of genomic testing was not prioritised for this guideline update as it has been the subject of a separate review by NICE. However, we appreciate the cross-over between the two guidelines and so have included a link to the NICE guideline on Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10).

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				[2] Risk can be estimated using a range of standardised tools based on clinical-pathological features, such as PREDICT, and clinical expertise [3] Indicated based on the results from gene expression profiling testing or judged to be advisable based on clinical expertise for patients not eligible for gene expression profiling testing	
Great Western Hospitals NHS Foundation Trust	Draft	16	1-8	I am concerned that NICE has made no mention at all about the use of intra-operative radiotherapy (IORT) in the management of early breast cancer. This is despite its acceptance by NICE for use in the NHS within centres that have the Intrabeam® equipment and established expertise in IORT use. The use of IORT has significant benefits for the patients including an immediacy of treatment, negating the three weeks of daily travel to and from a radiotherapy centre. This has economic and social benefits for the patients and carers. The use of this technology will reduce the pressure on existing radiotherapy centres and the reduction in travel by patients will reduce the carbon footprint of travel. The use of IORT has been demonstrated to be as effective in the control of local recurrence and may be associated with a lower risk of non-breast cancer mortality when compared with traditional radiotherapy methods. This technique is established within Europe and been accepted within the Medicare system in Australia and more recently approved by NICE. It seems ridiculous that a UK invented, developed and tested radiotherapy technique has not been mentioned. Patients increasingly demand information about other methods, treatments and techniques of managing their breast cancer. In the light of the recent Montgomery ruling this means that we cannot	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.

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				deny this treatment exists and that as clinicians we must be honest about its benefits and its availability.	
GreenVits	Draft	24	16-26	1.14 The effects of Omega-3 and Omega-6 on overall mortality after diagnosis of breast cancer should be considered again before this guidance is issued Higher intakes of EPA and DHA from dietary sources were reported to be associated with a 25% reduction in breast cancer recurrence and improved overall mortality in a large cohort of over 3,000 women with early stage breast cancer followed for a median of 7 years Target levels should be set to: **Omega-3 Index** >8% **Omega-6/3 Ratio** <3:1 (Good indicator for Inflammation from food sources) In 2016 NICE rejected any further study of Omega-3 and Omega-6 for this guidance. This was made despite significant evidence being offered at the time for the benefit of scientific measurement and adjustment of Fatty Acid blood levels. **Primary source:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4418048/ **Secondary sources:** http://www.expertomega3.com/omega-3-studies/oncology https://www.greenvits.eu/collections/omega-3 https://www.omegametrix.eu/wasistomega3index.html	Thank you for your comment. No evidence was found that demonstrated the effects of omega-3 and omega-6 on breast cancer recurrence so the committee were unable to make specific recommendations on this. For this evidence review, we prioritised RCT evidence over evidence from cohort studies as this is the most reliable evidence to assess efficacy and has the least susceptibility to bias. For dietary factors, evidence from RCTs was included, hence we could not include evidence from the cohort study quoted.
GreenVits	Draft	24	16-26	1.14 The effects of Vitamin D on overall mortality after diagnosis of breast cancer should be considered again before this guidance is issued	Thank you for your comment. The evidence review for this question focussed on the impact of lifestyle factors on recurrence, not mortality. No evidence was found that

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				Higher serum concentrations of 25(OH)D were associated with lower case-fatality rates after diagnosis of breast cancer. Specifically, patients in the highest quintile of 25(OH)D had approximately half the death rate from breast cancer as those in the lowest. Target levels for 25(OH)D for all patients with breast cancer should be set to at least 100-150 nmol/L Some doctors recommend aiming for 200 nmol/L during the treatment phase Vitamin D has a half-life in the body of 30-60 days, so dosage is required at least every 7-30 days. Vitamin D is fat soluble, so the dosage needs to be adjusted according to weight of the patient. In 2016 NICE rejected any further study of Vitamin D for this guidance. This was made despite significant evidence being offered at the time for the benefit of scientific measurement and adjustment of Vitamin D blood levels. **Primary source:** http://ar.iiarjournals.org/content/34/3/1163.long **Secondary sources:** https://grassrootshealth.net/document/scientists-call-to-daction/ https://www.vitamindwiki.com/Cancer+-+After+diagnosis https://www.vitamindcouncil.org/health-conditions/breast-cancer/	demonstrated the effects of vitamin D on breast cancer recurrence so the committee were unable to make specific recommendations on this.
Roche Products Ltd	Draft	7	5-7	Consider using a flow diagram to visually show the appropriate recommendations if the patient is clinically negative or clinically positive assessment at diagnosis, similar to Tari King's presentation on 'Individualising management of the nodes' presented at SABC 2017. The presentation provides clarity on	Thank you for your comment. The NICE pathway provides a visual representation of the recommendations in the guideline and may help to provide clarity on the management of positive or negative nodes.

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				what to do post-surgery and post-neoadjuvant treatment following an initial clinical assessment of the nodes at baseline.	
Roche Products Ltd	Draft	7	22-23	We are concerned that "regard these people as having node-negative breast cancer" is included under 'Evaluation and management of a positive axillary lymph node', without a clear definition within the guidelines. Suggest excluding this wording given that the objective of this section is not to define what node-positive vs node-negative looks like, but to suggest the most appropriate actions / care for patients who could potentially avoid axillary clearance.	Thank you for your comment. Recommendations 1.4.7 to 1.4.10 were all developed from an evidence review of further axillary treatment after primary surgery, which identified that in some groups no treatment after primary surgery was required, but these people would have initially have been identified as having a positive node. In addition, the definition of node-negative breast cancer is defined as those who only have isolated tumour cells. This is based on the American Joint Committee on Cancer (AJCC) cancer staging manual. This is explained in further detail in the abbreviations and glossary supplement that is provided with the guideline on the NICE website, as 'single cells or tiny clusters of cells no larger than 0.2mm'.
Roche Products Ltd	Draft	7	21	We are in agreement with the recommendation that axillary treatment should not be offered to all breast cancer patients but concerned that "isolated tumour cells" does not provide enough detail, and could be misinterpreted by clinicians thereby causing variance in the way this recommendation is implemented across the UK.	Thank you for your comment. The definition of isolated tumour cells is based on the American Joint Committee on Cancer (AJCC) cancer staging manual. This is explained in further detail in the abbreviations and glossary supplement that is provided with the guideline on the NICE website, as 'single cells or tiny clusters of cells no larger than 0.2mm'.
Roche Products Ltd	Draft	8	19	Consider including prognostic factors (such as nodal status at diagnosis) along with predictive factors as this is just as important for decision making and planning the appropriate care for the patient. It also helps guides clinicians conversations with their patient and set realistic expectations and may be more pertinent with the availabilities of treatments in the future.	Thank you for your comment. The predictive factors included in this section of the guideline (1.6) are only designed to form part of the prognostic factors that are used for decision-making and planning appropriate care. Additional recommendations on the factors to be taken into consideration are included in the section on adjuvant therapy planning.

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Royal College of General Practitioners	Draft	4	general	For completeness the short version of this guidance on diagnosis, referral and management of early breast cancer should include reference to the NG12 guidance on referral of suspected cancer. Also, the breast screening programme which identifies a significant proportion of early breast cancers should be referenced. The changes from the 2009 guidance are clearly identified and reasons for their inclusion clearly explained It would be helpful to identify those people at high risk for psychological late effects of breast cancer survivorship (young patients and those with more advanced disease) It may be helpful to consider the management of the menopause and associated clinical issues in breast cancer survivors The surgical management of breast cancer in BRAC mutation carriers does not appear to be covered	Thank you for your comment. NG12 and the breast screening programme are both referenced in the guideline (in the section called 'context'). Thank for your remark that the changes are clearly indicated in the updated guideline compared to the 2009 guideline. The proposal not to include the information and psychological support section of the guideline (1.2) in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we were only able to make changes to the wording of these recommendations to update terminology, but not to change the meaning. For example in 1.2.1 we changed the link to the most up to date NICE guidance on communication, in 1.2.2 we changed the words 'breast cancer nurse specialist' to 'clinical nurse specialist or other specialist key worker with equivalent skills'. Recommendations 1.2.4 and 1.2.5 were added as new recommendations for areas where the committee felt that more information was required – in the areas of clinical trials and fertility preservation. We have noted your comment on the management of the menopause and clinical issues in breast cancer survivors. This is covered in section 1.12 of the guideline, although this section was not included in this update. Risk-reducing options for people with BRCA mutation without breast cancer is not covered in the scope of this guideline. The recommendations for the surgical

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					management of the primary breast cancer in this guideline also apply to people with BRCA mutation who have breast cancer, and there should be a complete discussion of the risks and benefits with these people.
Royal College of General Practitioners	Draft	8	1	1.5 Breast Reconstruction: The guidance references immediate reconstruction of the affected breast, however the issue of surgery to the contralateral breast is an issue that commissioners are having to deal with and some guidance on that would be helpful. Is there any evidence for the place of surgery to the contralateral breast? Is there a variation in practice across the country?	Thank you for your comment. The committee did not specifically consider the evidence for contralateral breast surgery procedures, but we have added wording to the rationale and impact discussion about the importance of symmetry, so second mastectomy should be discussed as part of a consideration of breast reconstruction options to allow for symmetry.
Royal College of General Practitioners	Draft	8	15	5.3 Offering all options of breast reconstruction whether or not available locally. This is likely to be challenging, as it implies that options available elsewhere are possible to arrange.	Thank you for your comment. The recommendations on breast reconstruction have been amended to make it clear that both delayed and immediate reconstruction are viable options and both should be offered. To help discussions on the risks and benefits of both options, a preference sensitive decision point table has also been included, outlining some of the topics which should be included in the discussion and decision-making process. However, the committee agreed that all options should be available, and recognise that some units may need to change practice to achieve this.
Royal College of General Practitioners	Draft	13	8	1.8.4 Biological therapy: the use of Trastuzumab in cases of invasive breast cancer in the words of NICE's own evaluation is going to be "cost and resource intensive" The capacity of oncology centres to administer, as well as the commissioning of this very expensive drug will create challenges to its implementation, and may lead to variation in service provision across the country.	Thank you for your comment. Recommendation 1.8.4 was made in the previous guideline and was not reviewed for this update. There have been minor changes to the wording only to update it in line with the latest version of the Summary of Product Characteristics. Recommendation 1.8.5 is the new recommendation in this area in which it has been recommended that the use of trastuzumab is considered for patients with T1a/T1b HER2 positive tumours. The committee were aware that this would require an increase in resources but it was thought to be

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					an appropriate use of resources. Furthermore, the economic analysis conducted for the guideline suggested that the use of trastuzumab in this population was cost-effective.
Royal College of Nursing	General	General	General	The Royal College of Nursing (RCN) welcomes proposals by NICE to update the guidance for early and locally advanced breast cancer. The RCN invited members who care for people with breast cancer to review the draft document on its behalf. The comments below reflect the views of our reviewers.	Thank you for your comment and support for this guideline update. We appreciate your commitment to the stakeholder feedback process and would like to thank you for inviting comments from your members who care for people with breast cancer.
Royal College of Nursing	Evidence report B	22		Medical procedures on the treated side (lymphoedema management/risk) will be difficult to implement as there has been a historic recommendation for managing lymphedema, so it will require a lot of awareness raising to make clear that previously recommended practice has changed. There needs to be some work with MLD UK breast, breast cancer specialist nurses, doctors, physiotherapists, breast cancer charities, Manual Lymphatic drainage (MLD) therapists to change practice. For example, some therapists still recommend using hosiery for flying as preventative for lymphedema.	Thank you for your comment and for highlighting that a number of different organisations and practitioners will need to be involved to ensure implementation of this recommendation. The committee were aware that there was often concern about medical procedures affecting the treated side, but there is no consistent evidence for this. The aim of the recommendation was to increase consistency and reduce the number of people being declined immunisations or elective procedures due to venous access and improve access to standard care, such as blood tests at their local GP surgery.
Royal College of Pathologists	Draft	General	General	We welcome the changes in this updated-guidelines document. We support the use of progesterone receptor (PR) as a routine assay in breast cancer, with the following comments.	Thank you for your comment on this updated guideline and for your support for the use of progesterone receptor assays.
Royal College of Pathologists	Draft	6, 7	12-24, 1-3	A comment on further treatment of the axilla in cases with micrometastasis (or macrometastasis) in 1-2 nodes with extracapsular invasion is warranted.	Thank you for your comment. The proposal not to include the surgery to the axilla section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.

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Royal College of Pathologists	Draft	9	19-20	We think that recommending a "validated prognostic tools" is preferable than recommending a specific tool Predict. Predict can then be given as a recommended tool. Predict and Adjuvant!online and other online multiparameter prognostic tools have limitations and weakness and some oncologists may prefer to use more than one. Nottingham Prognostic Index can also be used to estimate prognosis. The sentence can read as follows: Use a validated prognostic tool such as PREDICT to estimate prognosis and the absolute benefits of adjuvant therapy for women with invasive breast cancer.	Thank you for your comment. The committee reviewed the evidence for the validity and prognostic efficacy of a number of available tools, including the Adjuvant Online and the Nottingham Prognostic Index. However. Adjuvant Online is no longer available and PREDICT was found to be the tool with the best evidence to support its use.
Royal College of Pathologists	Draft	12	5-6	DCIS is a heterogeneous disease with variable risk. There is no evidence to support using endocrine therapy for all low risk DCIS that are typically not candidate for radiotherapy. This recommendation may result mandatory use of ER to test all DCIS to determine ER status for further treatment. ER is currently not assessed in DCIS in most centres in the UK. These recommendations will make mandatory to test ER in all DCIS in addition these recommendation as such may result in over treatment of some patients. DCIS is currently comprising around 15% of screen detected-detected cancers making it approximately the third common cancer in women. Therefore, some comments on level of risk in these cases to be considered for ER assessment and endocrine therapy will be needed. Example: assess ER status and consider endocrine therapy for high risk ER-positive DCIS if radiotherapy is indicated but not received or for ER-Positive DCIS if radiotherapy is not indicated but the risk is not low or it is incompletely excised	Thank you for your comment. We agree that the benefits are greatest in people with higher risk and this is reflected in the recommendations, with endocrine therapy being offered only to patients who should have received radiotherapy but did not receive it (for whatever reason, including patient choice or comorbidities). In lower risk patients (those where radiotherapy was not recommended) endocrine therapy may be considered, but does not need to be offered. ER testing would only be required in people who are not having radiotherapy (for reasons of choice, comorbidities or because it is not required) and therefore the resource implications of extra ER tests will be minimal.
Royal College of Pathologists	Draft	13	8-24	A comment on using trastuzumab in elderly is needed. In some centres they don't offer it to older women?	Thank you for your comment. The recommendations on trastuzumab were not reviewed as part of this update and the committee did not review evidence for the use of trastuzumab in older women so we are unable to make the

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					change you have suggested. The amendments to these recommendations were to update them in line with the latest version of the Summary of Product Characteristics only.
Royal College of Pathologists	Draft	17	8-11	Does this mean offering radiotherapy to all DCIS regardless of risk and completeness of excision. (for instance, a small size (i.e., 5mm) low nuclear grade DCIS with 1cm margin, should radiotherapy be offered?)	Thank you for your comment. Radiotherapy following DCIS was not prioritised for this guideline update so the committee were unable to specify the groups that should not receive radiotherapy following DCIS. However, the committee noted that this recommendation led to some inconsistency with recommendations 1.7.10 and 1.7.11 and may lead to more radiotherapy given for DCIS than invasive cancer. Therefore, this recommendation has been amended to a 'consider' recommendation.
Royal College of Pathologists	Draft	19	1-4	Does this apply to all patients or to those with axillary clearance only excluding those with sentinel node biopsy?	Thank you for your comment. Recommendation 1.10.19 from the 2009 guideline refers to all patients.
Royal College of Physicians and Surgeons of Glasgow	General	N/A	N/A	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the United Kingdom who practice in the field of Breast Cancer. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this review of Early and Locally Advanced Breast Cancer: Diagnosis and Management by NICE. It recognises that management protocols need to change with changes in the understanding of disease, its assessment and its treatment. It recognises the importance of working with Patients to manage their disease.	Thank you for your comment. We appreciate your support for this guideline update and your commitment to good practice in the treatment of early breast cancer throughout the UK.
Royal College of Physicians	Draft	5	18	Most breast units will offer re-excision to patients who have tumour at the "inked" radial margin.	Thank you for your comment and for recognising that the evidence on margins is challenging. However, the

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and Surgeons of Glasgow				However the recommendations of the Association of Breast Surgeons guidelines suggest there should be a 1mm margin for both invasive breast cancer and DCIS. We are concerned that this may lead to inequity and inconsistency of treatment across units. We recognise the evidence of definite margins is challenging.	recommendation to offer re-excision at 0mm is based on the available evidence and is more permissive than the Association of Breast Surgeons guidelines (which are consensus-based), but not inconsistent with it
Royal College of Physicians and Surgeons of Glasgow	Draft	6	19	The recommendation of dual technique may already be outdated as many units have moved to a selective use of the dual technique where isotope signal is poor or in patients following neo-adjuvant chemotherapy or previous axillary surgery.	Thank you for your comment. The proposal not to include the surgery to the axilla section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.
Royal College of Physicians and Surgeons of Glasgow	Draft	7	5	Practice has moved in this area in response to US studies on the safety of post chemotherapy sentinel node biopsy in node positive cases. This recommendation does not take account of the use of selective use of sentinel node biopsy (in patients with biopsy proven nodal disease) following neo-adjuvant chemotherapy and clinical complete response.	Thank you for your comment. This question was not prioritised for inclusion in the guideline update and therefore were only able to make changes to the wording of these recommendations to update terminology, but not to change the meaning. However, the committee agreed that it was standard UK practice to carry out an ultrasound, and the following recommendation (1.4.7) clarifies that only people with a negative ultrasound-guided needle biopsy will go in to have sentinel lymph node biopsy. Sub-headings have also been added to the guideline to clarify the different population in recommendations 1.4.6 and 1.4.7.
Royal College of Physicians and Surgeons of Glasgow	Draft	7	8	While this outlines the POSNOC trial, it does not specifically take into account the recent extension of inclusion criteria for those patients who have positive nodes post neo-adjuvant chemotherapy.	Thank you for your comment. This recommendation does not exclude entry into the POSNOC trial. The guideline makes a general recommendation about inclusion into trials (1.2.4), and therefore inclusion into a trial could be discussed as part of any of the recommendations, where appropriate.

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Royal College of Physicians and Surgeons of Glasgow	Draft	8	2	Whilst many units offer immediate reconstruction, this recommendation will be a challenge for some who favour delayed reconstruction if the patient is to have radiotherapy. In particular, those units with high levels of implant use may need to change patient care pathways and operative choice with staff and other resource considerations.	Thank you for your comment. The recommendations on breast reconstruction have been amended to make it clear that no reconstruction may be the preferred option for some women. They have also been modified to make it clear that both delayed and immediate reconstruction are viable options and both should be offered. To help discussions on the risks and benefits of both options, a preference sensitive decision point table has also been included, outlining some of the topics which should be included in the discussion and decision-making process. However, the committee agreed that all options should be available, and recognise that some units may need to change practice to achieve this.
Royal College of Physicians and Surgeons of Glasgow	Draft	10	5	This has been a creeping extension of genetic testing which one of our reviewers suspects has not been costed or funded despite a recommendation in her region for the last 2 years where they have moved from testing <40 to <50 years.	Thank you for your comment. The genetic testing for BRCA1 and BRCA2 recommendations within the guideline were not prioritised for this guideline update, and no evidence was reviewed so we are unable to change this recommendation. However, an additional cross-reference has been included to the NICE familial breast cancer guidance, so the reader should refer to the most up to date NICE recommendations which define the thresholds for offering testing.
Royal College of Physicians and Surgeons of Glasgow	Draft	11	2	An extension of the use of ovarian suppression in pre-menopausal women will lead to an increase in clinic resources and the recommendation acknowledges this.	Thank you for your comment. The committee recognised that extending ovarian suppression would require an increase in resources. However, this was not anticipated to be a substantial cost increase due to the number of centres already offering ovarian function suppression. Further, increased costs will be at least partially offset by improvements in survival outcomes, and so this is thought to be a cost-effective use of resources.

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Royal College of Physicians and Surgeons of Glasgow	Draft	12	2	Currently endocrine therapy is used in very few cases of DCIS. This recommendation suggests to offer this in a higher risk group who should have radiotherapy but do not. This is a popular indication but if this should be" considered" in the wider group described, additional resources will be required to test ER receptors in DCIS. This will need adequate funding.	Thank you for your comment. ER testing would only be required in people with DCIS who are not having radiotherapy (for reasons of choice, comorbidities or because it is not required) and therefore the resource implications of extra ER tests will be minimal.
Royal College of Physicians and Surgeons of Glasgow	Draft	12	11	Given the increasing age and co-morbidities of patients this should be "consider" depending on these factors. Certainly, this additional chemotherapy in a wider group and the recommendation of more low dose but higher frequency regimes will have cost implications.	Thank you for your comment. This recommendation is to guide choice of which people should be given taxanes in addition to anthracyclines and not who should receive, or not receive, adjuvant chemotherapy. There was not enough evidence to specifically list sub-groups of people who could be safely excluded from receiving taxanes, but the recommendation in 1.8.1 to offer taxanes in addition to anthracyclines will still depend on the an assessment of the benefits and risks in individual patients, which are described in 1.8.2. . In addition to the factors listed in 1.8.2 we have included a preference sensitive decision point table to help people and clinicians make a decision about the use of taxanes. We agree that low dose higher frequency regimens may have some resource implications and have discussed this in our analysis of the impact of this recommendation.
Royal College of Physicians and Surgeons of Glasgow	Draft	14	9	A change in practice to extend trastuzumab therapy to small cancers has implications for staff and clinic resources, cost of drugs and increased follow-up cardiac studies. This will require funding.	Thank you for your comment. The committee were aware that extending the use of trastuzumab to patients with T1a/T1b HER2 positive tumours would require an increase in resources but it was thought to be an appropriate use of resources. Furthermore, the economic analysis conducted for the guideline suggested that the use of trastuzumab in this population was cost-effective.
Royal College of Physicians	Draft	14	16	One of our reviewers was disappointed that there are no specific recommendation on the length of bisphosphonate therapy which	Thank you for your comment. The duration of therapy was not included in the evidence review for adjuvant

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and Surgeons of Glasgow				has been a factor in the funding challenges and delayed implementation of this guidance in some regions.	bisphosphonates so the committee were unable to make any recommendations on this. Furthermore, the EBCTG meta-analysis did not find enough evidence to recommend a specific duration of therapy either.
Royal College of Physicians and Surgeons of Glasgow	Draft	15	5	Dexa Scanning should however be offered to patients who have other risk factors (eg Fracture, early menopause, concomitant steroid use) for the development of Osteoporosis as per other NICE guidance. Cross referencing is required.	Thank you for your comment. The bone health section of the guideline was not prioritised for this guideline update and so only minor wording changes to the recommendations can be made, not changes that alter the meaning. Thus changes to the recommendations on DEXA scanning cannot be made. However, the committee considered the suggestion to include a link to the NICE osteoporosis guidelines but agreed that this would not provide any additional information than that included in the specific guidance for breast cancer treatment induced bone loss, which is hyperlinked from the guideline.
Royal College of Physicians and Surgeons of Glasgow	Draft	17	8	There is sensible stratification of RT use in invasive cancer in the document but no mention of this for DCIS. There is no discussion or recommendation in >65 age group and low grade DCIS. Cost and morbidity savings would be made in this group.	Thank you for your comment. Radiotherapy following DCIS was not prioritised for this guideline update so the committee were unable to specify the groups that should not receive radiotherapy following DCIS. However, the committee noted that this recommendation led to some inconsistency with the recommendations in section 1.7 and may lead to more radiotherapy given for DCIS than invasive cancer. Therefore, this recommendation has been amended to a 'consider' recommendation.
Royal Marsden Hospital NHS Foundation Trust	Draft	N/A	General	We would suggest: Offer genetic testing for BRCA1 and BRCA2 mutations to women diagnosed with invasive breast cancer aged 40 years or younger. Rationale: NICE Familial Breast Cancer Guidance CG164 (updated March 2017) 1.5.11 states "Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a	Thank you for your comment. The genetic testing for BRCA1 and BRCA2 recommendations within the guideline were not prioritised for this update, and no evidence was reviewed so we are unable to change this recommendation. However, an additional cross-reference has been included to the NICE familial breast cancer guidance, so the reader should refer to the most up to date NICE recommendations which define the thresholds for

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				combined *BRCA1* and *BRCA2* mutation **carrier probability of 10% or more."** The POSH data (Lancet Oncology, Vol 19, February 2018) identified BRCA1/2 mutations in 12% (338/2733) of patients diagnosed aged 40 years and under. This is mirrored in RMH unpublished data with a 12% (56/463) detection rate in this group of patients.	offering testing. The POSH study will be forwarded to the NICE surveillance team for consideration when they next review CG164.
Royal Marsden Hospital NHS Foundation Trust	Draft	N/A	General	NICE Guidelines should be consistent with Inherited Cancer Test Directory from NHS England. Due for release 2/3/2018.	Thank you for your comment. It was the committee's view that the Inherited Cancer Test Directory is NHS England policy and covers what is being funded by the NHS, while the role of NICE guidelines is to make clinical recommendations based on the available evidence.
Royal Marsden Hospital NHS Foundation Trust	Draft	7	8-10	1.4.7 "Offer axillary treatment after SLNB to people with 1 or more macro Mets". This goes against ABS guidelines and Z11 trial 10 year results. Whilst 1.4.8 allows one to consider no further treatment:	Thank you for your comment. The committee were aware of the Association of Breast Surgeons guidelines, but that is a consensus document and the recommendation 1.4.7 is based on the evidence review conducted for this guideline. Furthermore, the committee did not believe the recommendations contradicted this document. Although the ACOSOG Z0011 10 year trial results support no further axillary treatment for people with macrometastatic disease, the committee decided against routinely recommending this approach due to risk of bias which is described in the full evidence report relating to this review (Evidence report B). In particular recruitment bias due to participants being randomised after the sentinel lymph node results were known, radiotherapy treatment fields being altered in people randomised to have ALND and some patients being given radiotherapy off protocol, as well as attrition bias because data for long-term complications were only available for a subset of participants. There was evidence

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					in support of axillary treatment for those with pathologically proven involvement of the axillary lymph nodes, the population referred to in 1.4.7 ('people who have 1 or more sentinel lymph node macrometastases') which allowed the committee to make an offer recommendation. But there were unclear benefits and risks of further axillary treatment for the lower risk subgroup in 1.4.8 with 1 or 2 sentinel lymph nodes who had also been advised to have whole breast radiotherapy and systemic therapy. While the subgroup in 1.4.8 would also be offered further axillary treatment the risks and benefits of no further axillary treatment should also be discussed as an option (ideally as part of a clinical trial).
Royal Marsden Hospital NHS Foundation Trust	Draft	7	11-13	1.4.8 The way it is worded seems to exclude mastectomy patients entry into POSNOC which is only clinical trial on offer here looking at this.	Thank you for your comment. At the moment there is no evidence following mastectomy so the committee could not make a specific recommendation for this group. However, the guideline makes a general recommendation abut inclusion into trials (1.2.4) and therefore inclusion into a trial could be discussed as part of any of the recommendations, where appropriate.
Royal Marsden Hospital NHS Foundation Trust	Draft	10	5-8	1.6.10 Suggest re-word: Offer genetic testing for BRCA1 and BRCA2 mutations to women under 50 years with triple-negative breast cancer , regardless of whether family history of breast or ovarian cancer.	Thank you for your comment. The genetic testing for BRCA1 and BRCA2 recommendations within the guideline were not prioritised for this guideline update, and no evidence was reviewed so we are unable to change this recommendation. However, an additional cross-reference has been included to the NICE familial breast cancer guidance, so the reader should refer to the most up to date NICE recommendations which define the thresholds for offering testing.
Royal Marsden Hospital NHS	Draft	10	10-12	1.7.1 The guidance mentions OFS but not the use of an AI with this; I think this should be recommended as an option for high risk pre-menopausal women with ER+ breast cancer, based on	Thank you for your comment. The use of ovarian function suppression in addition to endocrine therapy (which includes both tamoxifen and aromatase inhibitors) for

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Foundation Trust				SOFT/TEXT analyses which have been published, and the more recent longer term follow-up data from San Antonio 2017.	premenopausal women with ER-positive breast cancer is covered in recommendation 1.7.4
Royal Marsden Hospital NHS Foundation Trust	Draft	14,15	14-23, 1-19	1.9 What about adjuvant bisphosphonates to premenopausal women on OFS: good evidence from ABCSG 12 study: published NEJM 2009.	Thank you for your comment. The committee did not look at evidence for the sub-group of people on ovarian function suppression (OFS), so were unable to make any specific recommendations for this group. However, the recommendations as they stand do not exclude people on OFS.
Royal Marsden Hospital NHS Foundation Trust	Draft	14	1-8	1.8.7 This is more intensive cardiac monitoring than many centres: where the guidelines: British Journal of Cancer (2009) 100, 684 – 692 have been adopted. Could these at least be acknowledged even if counter to SPC?	Thank you for your comment. The existing recommendations on trastuzumab for people with T1c and above HER2-positive disease and the cardiac monitoring required were not reviewed for this update and the committee did not review evidence for cardiac monitoring when using trastuzumab so we are unable to make the changes you suggest. As we can only make minor changes to the wording and not the meaning of the recommendations, the information provided on trastuzumab, has however, been updated in line with the current Summary of Product Characteristics.
Royal Marsden Hospital NHS Foundation Trust	Draft	17	17-19	1.10.10 "Offer adjuvant postmastectomy radiotherapy to people with node-positive 17 (macrometastases) invasive breast cancer or involved resection margins. " The benefits in this population may be marginal and would have some concerns regarding this recommendation, given the limited evidence base (pending publication of the SUPREMO trial results).	Thank you for your comment. The committee agree that this may represent over-treatment and that future data from the SUPREMO trial may help address this. However, subsequent recommendations do define the populations in more detail, and allow the option of not carrying out post-mastectomy radiotherapy in those with low risk. The evidence available to the committee did not allow a distinction to be made for the benefit of radiotherapy in people with 1 to 3 positive nodes, compared to those with 4+ positive nodes. Reduced loco-regional recurrence was seen in women with 1 to 3 positive nodes who were given radiotherapy, even when the tumour size was small (0 to

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					19 mm), and there was no difference in magnitude of this effect compared with medium or larger tumours. Furthermore, the magnitude of difference seen with radiotherapy in the evidence reviewed by the committee was not smaller for 1-3 nodes (14% difference in recurrence, RR=0.24) compared to 4+ nodes (11% difference in recurrence, RR=0.39)
Royal Marsden Hospital NHS Foundation Trust	Draft	24	1-3	*1.13.3 "Do not offer ultrasound or MRI for routine post-treatment surveillance in people who have had treatment for invasive breast cancer or DCIS". Would it not be reasonable to offer USS (or possibly MRI) follow-up in those with breast cancer which is apparently occult on mammographic imaging.*	Thank you for your comment. The proposal not to include the follow-up imaging section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest.
Royal Marsden Hospital NHS Foundation Trust	Draft	33	19	"The evidence showed no benefit in terms of disease-free survival or overall survival from continuing tamoxifen beyond 5 years". We do not agree with this statement. The ATLAS trial, published in the Lancet 2013 demonstrates an improvement in breast cancer mortality and OS. What more evidence is needed?	Thank you for your comment. When data from the ATLAS trial was meta-analysed with other studies that compared greater than 5 years of tamoxifen with 5 years of tamoxifen, there was no significant benefit of continuing tamoxifen. However, the committee agreed that greater weight should be given to the ATLAS study due to the age of the other trials. Therefore, it was recommended that extended tamoxifen is considered despite the non-significant benefit observed.
UK Breast Cancer Group	General	General	N/A	Comments/feedback from UKBCG As a general comment, We congratulate the Committee for a long-awaited update that reflects the real world choices of UK oncologists and aligns it with international guidelines. Due to the fast pace of research resulting in continuous improvements of standards of care, We would strongly recommend that guidelines are updated, ideally with a yearly review. If this is not feasible for NICE, they should indicate clearly that the recommendations are to be considered valid at the time of publication. UK clinicians	Thank you for your comment and support for this guideline update. We agree that there are limitations in the guideline process as each topic takes time to update. However, the NICE surveillance teams schedule regular checks for new evidence, which can bring forward an update. In addition, the technology appraisal programme at NICE permits new treatments to be considered outside of the guideline update process. We appreciate that this is

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				should be encouraged consult with other, more frequently updated sources such as ASCO, ESMO, NCCN guidelines. There is a serious risk that important developments will be held back as a result of outdated guidance becoming an obstacle to progress rather than a tool to guide up to date best practice. Without a clear statement that new evidence can have immediate impact on clinical recommendations. We offer the following specific comments:	an important clinical area affecting many people and where research is ongoing. The guideline is clearly marked with the date of publication and each recommendation is labelled with the year that it was published. NICE guidance is not intended to replace clinical judgement.
UK Breast Cancer Group	Draft	4	2-13	1.1 Does not have any guidance on imaging of the breast in young women (<30 or 35) and those with dense breasts on mammogram, who should have an US instead or in addition to mammography.	Thank you for your comment. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. The committee did not therefore review any evidence for imaging and we are unable to change these recommendations. However, the recommendations already state that ultrasound should be used in addition to mammography in those with dense breasts.
UK Breast Cancer Group	Draft	7	5-7	1.4.6 Offer axillary node clearance to women with a pre-op pathologically proven node positive breast cancer This maybe over treatment in some cases compared to where sentinel node positivity is proven post operatively. There is currently an absence of convincing data to suggest this is a different group if diagnosed with careful pre-operative assessment. However If bulky (clinically palpable) axillary disease is present, this is less likely to be eradicated by radiotherapy. It is recommended that most node positive patients have consideration for further treatment to dissected nodes, such as surgery or nodal radiotherapy. In a patient with pre-operative pathological node positive disease, who is rendered node	Thank you for your comment. The proposal not to include recommendation 1.4.6 in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we were able to update the recommendation wording but were not able to make any changes which altered the meaning. However, the committee recognised that there are ongoing trials in this area.

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				negative as indicated by post chemotherapy guided nodal sampling. The benefits of further post-operative treatment to the nodes, surgery or radiotherapy, may be small. If further treatment to potential microscopic disease to the axilla is recommended, nodal radiotherapy has less long term morbidity, especially lymphedema. This is a controversial area with new data emerging on a regular basis and access to more complex radiological/surgical management in a state of fast evolution. The value of guidance in this area is questionable as access to more complex techniques becomes more widespread. Consideration should be given to more complex axillary localisation pre operatively. The involved node can be clipped prior to any neoadjuvant chemotherapy so that it can be identified post neoadjuvant treatment. Identification of involved nodes post chemotherapy maybe less accurate using standard sentinel node identification techniques.	
UK Breast Cancer Group	Draft	11	16-19	1.7.7 Extended adjuvant endocrine therapy The longer term benefits of extended adjuvant endocrine therapy are not yet known as the follow up in many studies evaluating its use is short. However low risk patients (i.e. node negative patients) are unlikely to derive much benefit but use its use should be considered if other high risk relapse factors can be identified. In all patients offered extended endocrine therapy, a discussion involving all relevant factors should be considered. These include risk factors of long term recurrence, likely life expectancy of patient, co-morbid conditions, tolerance to current and any previous endocrine therapy, bone density, risks for blood clots, endometrial cancer and vascular risk factors.	Thank you for your comment and for suggesting factors that need consideration when considering the risks and benefits of extended endocrine therapy. The committee agreed that the risks and benefits of endocrine therapy were important and a preference sensitive decision point table has been included in the guideline to assist with the discussion of risks and benefits of extended endocrine therapy.

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UK Breast Cancer Group	Draft	12	7-9	1.7.11 DCIS ENDOCRINE THERAPY There is no demonstrated survival benefit for endocrine therapy in patients with DCIS. The absolute benefit is likely to be very small for most patients, and limited to those with higher risks (high grade disease), those who don't have radiotherapy and with long life expectancies. The benefits are only in reductions in local recurrence and contra lateral new primaries, and have to be carefully balanced against well-documented side effects of hormonal therapy. There is a huge variation between centres in the UK of use of radiotherapy after resection of DCIS from almost all patients in some, to almost none in others. Trials evaluating all aspects of treatment of DCIS should be strongly encouraged (eg LORIS) but much work is needed on which patients benefit from any further treatment.	Thank you for your comment. We agree that the benefits are greatest in people with higher risk and this is reflected in the recommendations, with endocrine therapy being offered only to patients who should have received radiotherapy but did not receive it (for whatever reason, including patient choice or comorbidities). In lower risk patients (those where radiotherapy was not recommended) endocrine therapy may be considered, but does not need to be offered. We agree that trials should be encouraged and have made an over-arching recommendation at the beginning of the guideline (1.2.4) stating this.
UK Breast Cancer Group	Draft	12	11-13	1.8.1 Adjuvant chemotherapy The recommendation that all patients should be offered an anthracycline and a taxane will be over treatment for many. In higher risk patients we agree. However in lower risk groups such as node negative or small nodal burden, favourable biology (er+her-) where the benefits of chemotherapy is smaller, then regimes such as docetaxol/cyclophosphamide x4, epirubicin (or adriamycin)/cyclophosphamide x4 are appropriate and should be considered as acceptable options. The use of weekly or 2 weekly paclitaxel x4 (weekly often given as weekly 3 out of 4 x4) is standard is definitely less toxic than	Thank you for your comment. There was not enough evidence to specifically list sub-groups of people who could be safely excluded from receiving taxanes, but the recommendation in 1.8.1 to offer taxanes in addition to anthracyclines will not necessarily result in over-treatment as the decision will still depend on the an assessment of the benefits and risks in individual patients, which are described in 1.8.2. . In addition to the factors listed in 1.8.2 we have included a preference sensitive decision point table to help people and clinicians make a decision about the use of taxanes.

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				docetaxel 3 weekly. However many centres are not be able to offer this due to resource implications.	
UK Breast Cancer Group	Draft	13, 14	1-13, 8-11	1.8.1/1.8.4 Biologicals Trastuzumab should be offered to patients with her2 + disease. Patients at low risk (t1a/b) node negative, will have a low risk of recurrence , despite being her2+, treatment of all such cases would be over treatment such as ER positive cases but appropriate for instance for ER negative or high grade disease . In low risk patients with her2+ disease who are recommended chemotherapy and trastuzumab, then consideration should be given to weekly paclitaxelx12 and trastuzumab, to minimise toxicity.	Thank you for your comment. There was insufficient sub-group data to safely exclude specific groups, but the recommendation for people at low risk of disease is a consider recommendation, and includes details on consideration of comorbidities, prognostic features and toxicity, so it is not intended that trastuzumab would be given to all people with T1a/T1b disease.
UK Breast Cancer Group	Draft	14, 15	14-23, 1-19	Adjuvant Bisphosphonates 1.9 In the trials there was benefit in all patient groups. A large biologically aggressive node negative breast cancer may derive more benefit than a small unaggressive node positive one. Again the risk benefit ratio should be assessed in all patients, depending on risk of relapse, taking into consideration all other factors such as other treatments given and bone density in low to moderate risk patients. These patients may well be recommended bisphosphonates anyway if they have osteopenia/osteoporosis. Suggested regimes, such as zolendronic acid 6 monthly x 6 for 3 years could be recommended.	Thank you for your comment. There was not consistent evidence of benefit in all groups; there was stronger evidence in the node-positive and postmenopausal group so the recommendation is an offer recommendation for this group. However, a consider recommendation was made for other high-risk postmenopausal women to reflect that some node-negative patients may benefit and to allow consideration of other factors. Recommendation 1.9.3 ensures that a discussion of the risks and benefits for individual people is undertaken. There was insufficient evidence available to the committee to recommend a specific dosing regimen as this was not part of the question under consideration.
UK Breast Cancer Group	Draft	14	1-8	1.8.7 Cardiac monitoring. The benefits of adjuvant trastuzumab are now well documented from many studies. A 55% ejection fraction cut off in trials was	Thank you for your comment. The existing recommendations on trastuzumab for people with T1c and above HER2-positive disease and the cardiac monitoring required were not reviewed for this update and the

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				appropriate when the benefits of adjuvant her2 directed therapy was unknown, alongside unknown levels of cardiac toxicity. Now the benefits are realised with trastuzumab and pertuzumab, a less stringent approach needs to be considered. This would involve taking into account in each patient, the benefits and risks, as well as the type of chemotherapy used. Non-Anthracycline containing regimes are equally effective, with minimal cardiac toxicity. For Instance a patient with a large node positive her2 positive cancer has a very poor outlook without systemic her2 based therapy. If their ejection fraction was below 55% but within institutional normal range, the cardiac safety of short course anthracycline/taxane or non-anthracycline containing regime is well established and would be a very reasonable treatment. Cardiac monitoring is standard. Also the standard UK monitoring of cardiac function does not recommend 3 monthly assessments. It is one pre chemo, one at 3 months, repeated again once again 3 months later. If no drop, no need to repeat again. Cardiac monitoring is not recommended or needed post trastuzumab cessation unless clinically indicated. If the patients EF drops below 40% then recommend suspend her2 based therapy, add an ace inhibitor, assess patient by ECHO or MUGA and refer to cardiologist. Consider restarting her2-based therapies depending on improvement in cardiac function, risk of relapse and duration of treatment left.	committee did not review evidence for cardiac monitoring when using trastuzumab so we are unable to make the changes you suggest. As we can only make minor changes to the wording and not the meaning of the recommendations, the information provided on trastuzumab, has however, been updated in line with the current Summary of Product Characteristics.
UK Breast Cancer Group	Draft	16	1-8	1.10.2 Consider partial breast radiotherapy in selected cases. This should be strongly encouraged. As per IMPORT LOW trial The technique recommended should be as in the IMPORT LOW protocol, with the use of surgical clips placed at the time of surgery.	Thank you for your comment. The criteria for partial breast radiotherapy specified match the IMPORT-LOW protocol as you have suggested. A stronger recommendation was not made as IMPORT LOW has not yet reached 10 year follow-up and the committee agreed that differences in local recurrence may become evident with longer follow-up. The committee were aware that while localization of

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					the tumour bed was most commonly carried out using clips there were other techniques which could be used. As the committee did not look at the evidence comparing these different techniques they were unable to make specific recommendations in this area.
UK Breast Cancer Group	Draft	16	18-25	1.10.5 Consider omitting radiotherapy for women who: such as over 60 years old, t1, g1-2 node negative er+ her-. Support of ongoing studies such as PRIMETIME should be encouraged to further explore the risk of local recurrence in the modern era, using molecular subtyping techniques. Please can it be made absolutely clear that any reference to lack of survival benefit with radiotherapy refers to a small, highly selected group of older women with very low risk breast cancer and this should not be applied to the wider population of women with breast cancer. Also, please can the statement that radiotherapy gives no increase in serious late effects be clarified by adding as long as the heart/lung doses are kept within reasonable limits and the patient has no significant cardiac risk factors or is a smoker (Taylor et al JCO 2018 can be referenced here).	Thank you for your comment. The evidence to lower the age limit to 60 for omitting radiotherapy does not yet exist - although the committee agreed this may be available when the PRIMETIME study is completed. The committee encouraged recruitment to clinical studies throughout the guideline with an over-arching recommendation (1.2.4). The lack of survival benefit does refer to the small group of older women, and the wording of the recommendation has been amended to make this clearer. Finally, the recommendation about minimising the dose of radiotherapy to the heart and lungs has been moved to the beginning of the radiotherapy section to make sure it is clear that it applies to this whole section.
UK Breast Cancer Group	Draft	16	15-17	1.10.4 Interstitial /intraoperative radiotherapy. This should be offered (as recommended in USA/Europe) only to very low risk patients, and with explanation that it may well lead to an increase in local recurrence risk. The follow up of the TARGIT and other intraoperative trials is widely accepted as too short for to evaluate adequately, with a recurrence risk similar to trials where no Radiotherapy was offered (PRIME). It should generally only be offered as part of a well designed prospective trial	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy, as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.

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UK Breast Cancer Group	Draft	17	8-11	1.10.7 Considerable variation here. Support statement that trials exploring the benefits should be encouraged	Thank you for your comment. There is now an over-arching recommendation to consider entry into clinical trials wherever possible, at the beginning of the guideline.
UK Breast Cancer Group	Draft	17	17-19	1.10.10 Post mastectomy radiotherapy 1.10.10 In 1-3 node groups. Considerable controversy here and results of supremo trial are awaited. Some patients will benefit, but generally those with other risk factors, such as young age (under 50), grade 3, larger tumours, and extensive lymphovascular involvement. See comments from supremo team Offer post mastectomy radiotherapy to people with node positive (macro metastases) invasive breast cancer….' In the Rationale and impact of this recommendation, it is stated that 'this is because the evidence showed a beneficial effect on survival and local recurrence. Although the evidence was limited the committee acknowledged that radiotherapy is associated with lung and cardiac morbidity, they concluded that for this group of women, the benefits of radiotherapy outweigh the harms….'. We believe that this recommendation does not reflect a balanced interpretation of the clinical evidence. In their assessment of the recommendation on practice, it is stated: 'the committee agreed the recommendations will reinforce current practice, so there would be little change in practice'. We do not believe this statement is an accurate reflection of current practice since postmastectomy radiotherapy is not standard care for all UK centres for patients with 1-3 nodes positive. The previous NICE guidance on postmastectomy radiotherapy (PMRT) CG80 (2009) stated: 1.1.11.4 Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an	Thank you for your comment. The committee agree that this may represent over-treatment and that future data from the SUPREMO trial may help address this. However, subsequent recommendations do define the populations in more detail, and allow the option of not carrying out post-mastectomy radiotherapy in those with low risk. The evidence available to the committee did not allow a distinction to be made for the benefit of radiotherapy in people with 1 to 3 positive nodes, compared to those with 4+ positive nodes. Reduced loco-regional recurrence was seen in women with 1 to 3 positive nodes who were given radiotherapy, even when the tumour size was small (0 to 19 mm), and there was no difference in magnitude of this effect compared with medium or larger tumours. Furthermore, the magnitude of difference seen with radiotherapy in the evidence reviewed by the committee was not smaller for 1-3 nodes (14% difference in recurrence, RR=0.24) compared to 4+ nodes (11% difference in recurrence, RR=0.39). The evidence on 1-3 nodes for patients treated with mastectomy and axillary dissection was not dominated by the DBCG data; this only contributed 25% of the weight to the analysis and there is still significantly reduced locoregional recurrence following post-mastectomy radiotherapy if the DBCG data is excluded from the analysis.

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				intermediate risk of local recurrence into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40. We assume that the guideline committee has been strongly influenced in extending the recommendation to patients with 1-3 positive nodes by the results of the EBCTCG meta-analysis of postmastectomy radiotherapy (McGale et al, Lancet 2014; 383:2127-3135). Of the 1314 patients with 1-3 positive nodes treated with mastectomy and axillary dissection, there was an 11.5% absolute reduction in first recurrence and a 20 year reduction in breast cancer mortality of 7.9% (both p=0.01). Little or no account seems to have been taken of the following factors in relation to the interpretation of the 2014 EBCTCG meta-analysis of PMRT which in our view limits the generalisability of the findings to contemporary practice: • The subset of patients with 1-3 positive nodes is dominated by the Danish Breast Cancer Cooperative Group trials in which it is well recognized that the loco-regional rates were very much higher than in more contemporary series. Professor Jay Harris (Boston) points out in a recent viewpoint article 'Treatment of regional nodes in breast cancer – not recommended for all patients with 1 to positive nodes (JAMA Oncology 2016; 2:991-992) that 'the loco-regional recurrence rate in unirradiated patients was 16.5% at 5 years and 20.3% at 10 years. These rates are substantially higher than seen currently in the United States and elsewhere'. • Absence of stratification for molecular subtype • Small sample size of patients who received chemotherapy and endocrine therapy	

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				• LRR and OS survival advantages of modern endocrine and anti-HER2 therapy are not considered (Olial C & Hurvitz SA, Nat Rev Clin Oncol 2015; 12:567-8. • In most of the trials patients were randomised to PMRT were treated by comprehensive loco-regional irradiation whereas the SUPREMO trial assesses the role of chest wall irradiation (acknowledged in the discussion of the meta-analysis). Neither the 2017 St Gallen guidelines (Curigliano et al, Ann Oncol 2017;28:1700-2017) nor 2016 guidelines of the American Society of Clinical Oncology/American Society for Radiation Oncology and Society of Surgical Oncology (J Recht et al, JCO 6911188,2016) advocate PMRT for all patients with 1-3 nodes positive. With contemporary standards of systemic therapy, the risks of local and distant recurrence may be lower. This is acknowledged by the authors of the 2014 EBCTCG in the discussion of the meta-analysis of PMRT: 'Furthermore, many women now receive better systemic therapy that is more effective at treating both local and distant disease. Therefore the absolute risk of a recurrence is likely to be lower for women being considered for postmastectomy radiotherapy today than for the women in these trials and the absolute risk reductions achieved with radiotherapy are also likely to be smaller.' The MRC/SUPREMO trial has collected data on 1688 patients internationally with 1-3 positive nodes or node negative with other risk factors with quality assured contemporary surgery and systemic therapy with or without chest wall irradiation. This includes ER, PgR and HER-2 status and data on adjuvant chemotherapy, hormonal therapy and anti-HER2 therapy. The median follow up of the trial is now 90 months (7.3 years). The TRANS-SUPREMO sub study with tumour samples on over 1300 patients provides the opportunity to identify which biological	

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				factors influence the response to radiotherapy and refine selection of patients for PMRT in the future. We are not in position to report the results at present. However we can say that at this stage the event rates is low with a current survival rate for all patients >85%. This is clearly a lot higher than the patients included in the trials in the EBCTCG overview. We would contend that the evidence base is not sufficient to recommend PMRT for contemporary patients with 1-3 nodes (macrometastases) to improve overall long-term survival. We appreciate your continuing support for following up patients in the MRC/EORTC SUPREMO trial up to at least 10 years so that we can provide robust evidence to inform clinical practice both in the UK and worldwide	
UK Breast Cancer Group	Draft	17	14-15	1.10.9 Use of deep breathe hold and other techniques should be encouraged. This is especially pertinent in patients in whom excess heart/lung volumes are included, despite techniques such as partial breast radiotherapy, and angling of tangents and or IMRT. It should also be employed if the internal mammary chain is being irradiated on either side.	Thank you for your comment. We agree that deep breath techniques should be encouraged, and this recommendation has been moved to the start of the radiotherapy section so it is clear that it applies to the whole radiotherapy section.
UK Breast Cancer Group	Draft	18	9-11	1.10.14 Boost. Further statements on which patients should have a boost, such as young age (under 50, grade 3, extensive lymphovascular invasion).Patients over the age of 60 should rarely require a boost	Thank you for your comment. The proposal not to include the breast boost following breast-conserving surgery section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update only minor wording changes to the recommendation can be made and we are not able to make changes that alter the meaning.
UK Breast Cancer Group	Draft	18	19-20	1.10.17 Agree unless disease remains un resected post clearance	Thank you for your comment. The proposal not to include the radiotherapy to nodal areas section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update only minor wording

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					changes to the recommendation can be made and we are not able to make changes that alter the meaning.
UK Breast Cancer Group	Draft	19	5-7	1.10.20 IMC chain irradiation should be considered for patients with node positive disease, especially if 3 or more nodes and involved and or other adverse features, such as grade 3, adverse subtypes. However breathe holding, or other techniques should be employed as standard to reduce heart and lung dose. Otherwise any gain in disease control/eradication will be offset by increased toxicity.	Thank you for your comment. We have reordered the recommendations so that those that advise deep breath hold techniques and other techniques to reduce the dose to the heart and lungs are at the beginning of the radiotherapy section. This makes it clearer that they apply to all subsequent recommendations, including those on irradiation of the internal mammary chain.
UK Breast Cancer Group	Draft	23	9-12	1.12.12 Use of SSRI inhibitors on reducing effectiveness of Tamoxifen is very weak and largely been disproven. Withholding use of tamoxifen in conjunction with SSRIs may reduce compliance with hormonal therapy or adversely impact on effective treatment of mental disorders.	Thank you for your comment. The proposal not to include the menopause symptoms section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest. However, the committee were aware that the use of SSRIs is not recommended in conjunction with tamoxifen in the current Summary of Prescribing Characteristics and so could not update this recommendation on that basis.
University College London	Draft	General	General	The following comments are about a) Use of Preoperative MRI b) Use of preoperative Axillary US and sampling c) Reconstruction d) Neoadjuvant chemotherapy and e) Intraoperative radiotherapy f) Lifestyle advice In the name of transparency and evidence based medicine, every recommendation in the NICE guidance should ideally be	Thank you for your comment and feedback about the NICE guideline process. NICE does not annotate recommendations (as outlined in the methods manual), rather we use 'offer' and 'consider' to reflect strength of a recommendation. The short guideline now includes rationale and impact sections so that readers can quickly find the reasoning behind recommendations. These sections then refer to the full evidence reports, which include summaries of the evidence, the GRADE tables (in which the quality of the evidence is rated by outcome and used to inform the strength of the recommendations), full reference lists and committee discussions: these are

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				annotated with the level of evidence supporting it along with the list of references. The rationale section should include an evidence based response, giving scientific reasons for accepting or not accepting the comments received in the public consultation	amended following the receipt of stakeholder comments as necessary. In addition the responses to all the stakeholder comments are published on the NICE website as a record of which comments resulted in changes to the guideline, and which did not.
University College London	Draft	General	General	References for all the comments are listed below: 1. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010;375(9714):563-71. doi: 10.1016/S0140-6736(09)62070-5 2. StatBite: Trends in mastectomy and preop MRI rates at the Mayo Clinic. *Journal of the National Cancer Institute* 2009;101(24):1668. doi: 10.1093/jnci/djp451 3. StatBite: Association between mastectomy rates and MRI use at Mayo Clinic. *Journal of the National Cancer Institute* 2008;100(15):1053. doi: 10.1093/jnci/djn273 4. Bleicher RJ, Ciocca RM, Egleston BL, et al. Association of routine pretreatment magnetic resonance imaging with time to surgery, mastectomy rate, and margin status. *Journal of the American College of Surgeons* 2009;209(2):180-7; quiz 294-5. doi: 10.1016/j.jamcollsurg.2009.04.010 5. Morrow M, Keeney K, Scholtens D, et al. Selecting patients for breast-conserving therapy: the importance of lobular histology. *Cancer* 2006;106(12):2563-8. doi: 10.1002/cncr.21921 6. Solin LJ, Orel SG, Hwang WT, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. *Journal of clinical oncology : official*	Thank you for your comment and for sending these references. We will respond to them in the comments table where they are referenced in context, but have also included a summary below explaining, if appropriate, why they were not included in our evidence review: 1 to 7: relate to MRI which was not prioritised for review in this update 8: studies included in this meta-analysis were included in our review where they were consistent with the review protocol 9: related to axillary treatment which was not prioritised for review in this update 10, 11, 12: did not meet the protocol for the comparison of immediate versus delayed reconstruction 13: this Cochrane review was checked for relevant studies but not included in its entirety due to the comparisons with no reconstruction 14: book chapters were not in the search protocols for our evidence reviews 15, 16, 17: did not meet the protocol for the comparison of immediate versus delayed reconstruction 18: was not included in the review as it compared radiotherapy and no radiotherapy, rather than partial and

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				journal of the American Society of Clinical Oncology 2008;26(3):386-91. doi: 10.1200/JCO.2006.09.5448 7. Pilewskie ML, Olcese C, Eaton A, et al. Association of MRI and locoregional recurrence (LRR) rates in ductal carcinoma in situ (DCIS) patients treated with or without radiation therapy (RT). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(suppl 26) 8. Vaidya JS, Bulsara M, Wenz F, et al. Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *International journal of radiation oncology, biology, physics* 2016;96(2):259-65. doi: 10.1016/j.ijrobp.2016.05.008 9. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA : the journal of the American Medical Association* 2017;318(10):918-26. doi: 10.1001/jama.2017.11470 10. Harcourt D, Rumsey N, Ambler N, et al. The psychological effect of mastectomy with or without breast reconstruction: A prospective, multicentre study. *Plastic & Reconstructive Surgery* 2003;111(3):1060-68. 11. Potter S, Brigic A, Whiting P, et al. Reporting clinical outcomes of breast reconstruction. A systematic review. *Journal of the National Cancer Institute* 2011;103(1):31-46. 12. Potter S, Harcourt D, Cawthorn SJ, et al. Assessment of cosmesis after breast reconstruction surgery: A systematic review. *Annals of Surgical Oncology* 2011;18(3):813-23.	whole breast radiotherapy and there were no data on the subgroup of smokers 19-25: relate to the use of intraoperative radiotherapy which was not included in our review as it is covered by other NICE guidance 26: relates to interstitial brachytherapy which has now been removed from the recommendations 27: was not included in the review as it compared radiotherapy and no radiotherapy, rather than partial and whole breast radiotherapy; 28 and 29: were not considered due to study design (non-RCT) 30: was a letter to an editor so was not included in the evidence review 31: published after the cut-off date for our search (although most of the applicable studies in this meta-analysis were

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				13. D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. *Cochrane database of systematic reviews* 2011(7):CD008674. doi: 10.1002/14651858.CD008674.pub2 14. Vaidya JS. The Systemic Effects of Local Treatments (Surgery and Radiotherapy) of Breast Cancer. In: Retsky M, Demichelli R, eds.: Nature, Springer 2017. 15. Beecher SM, O'Leary DP, McLaughlin R, et al. Influence of complications following immediate breast reconstruction on breast cancer recurrence rates. *Br J Surg* 2016;103(4):391-8. doi: 10.1002/bjs.10068 16. Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *The lancet oncology* 2016 doi: 10.1016/S1470-2045(16)30668-4 17. Dillekas H, Demicheli R, Ardoino I, et al. The recurrence pattern following delayed breast reconstruction after mastectomy for breast cancer suggests a systemic effect of surgery on occult dormant micrometastases. *Breast cancer research and treatment* 2016;158(1):169-78. doi: 10.1007/s10549-016-3857-1 18. Taylor C, Correa C, Duane FK, et al. Estimating the Risks of Breast Cancer Radiotherapy: Evidence from Modern Radiation Doses to the Lungs and Heart and from Previous Randomized Trials. *Journal of Clinical Oncology* 2017;35(15):1641-49. 19. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast	identified by our literature review and included in the evidence review). 32: was not considered due to study design (non-RCT) 33: is an animal study 34: is a commentary 35: did not compare neoadjuvant chemotherapy with no neoadjuvant chemotherapy. 36: published after the cut-off date of our search (and would not have been included as it is a non-systematic review) 37: related to the development of new breast cancer, not recurrence 38: in vitro study 39: related to the development of new breast cancer, not recurrence 40: related to mortality, not recurrence

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				radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383(9917):603-13. doi: 10.1016/S0140-6736(13)61950-9 20. 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) doi: 10.3310/hta20730 21. Vaidya JS, Bulsara M, Wenz F, et al. Targeted radiotherapy for early breast cancer. *Lancet* 2018;391(10115):26-27. doi: 10.1016/S0140-6736(17)33316-0 [published Online First: 2018/01/13] 22. Corica T, Nowak AK, Saunders CM, et al. Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial. *International journal of radiation oncology, biology, physics* 2016;96(1):55-64. doi: 10.1016/j.ijrobp.2016.04.024 23. 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. doi: 10.1136/bmjopen-2015-010703 24. Vaidya A, Vaidya P, Both B, et al. Health economics of targeted intraoperative radiotherapy (TARGIT-IORT) for early breast cancer: a cost-effectiveness analysis in the United Kingdom. *BMJ open* 2017;7(8):e014944. doi:	

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				10.1136/bmjopen-2016-014944 [published Online First: 2017/08/19] 25. Vaidya JS, Wenz F, Tobias JS. Trial supports targeted radiotherapy for early breast cancer but protocol still requires 3 weeks of daily therapy. *BMJ Evid Based Med* 2018;23(1):38-39. doi: 10.1136/ebmed-2017-110849 [published Online First: 2018/01/26] 26. Vaidya JS, Bulsara M, Wenz F, et al. Partial breast irradiation and the GEC-ESTRO trial. *Lancet* 2016;387(10029):1717. doi: 10.1016/S0140-6736(16)30255-0 27. Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2016;121(3):402-13. doi: 10.1016/j.radonc.2016.08.017 [published Online First: 2016/09/19] 28. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2015;114(1):56-65. doi: 10.1016/j.radonc.2014.10.004 [published Online First: 2014/12/03] 29. Darby SC, Ewertz M, McGale P, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *New England Journal of Medicine* 2013;368(11):987-98. doi: 10.1056/NEJMoa1209825	

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				30. Vaidya JS, Bulsara M, Wenz F. Ischemic heart disease after breast cancer radiotherapy. *New England Journal of Medicine* 2013;368(26):2526-27. doi: doi:10.1056/NEJMc1304601 31. Early Breast Cancer Trialists' Collaborative G. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *The lancet oncology* 2018;19(1):27-39. doi: 10.1016/S1470-2045(17)30777-5 [published Online First: 2017/12/16] 32. Killelea BK, Yang VQ, Mougalian S, et al. Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. *Journal of the American College of Surgeons* 2015;220(6):1063-9. doi: 10.1016/j.jamcollsurg.2015.02.011 [published Online First: 2015/04/15] 33. Karagiannis GS, Pastoriza JM, Wang Y, et al. Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. *Sci Transl Med* 2017;9(397) doi: 10.1126/scitranslmed.aan0026 [published Online First: 2017/07/07] 34. Swanton C. Cancer therapeutics through an evolutionary lens. *Journal of the Royal Society of Medicine* 2018;111(1):8-14. doi: 10.1177/0141076817742096 [published Online First: 2018/01/18] 35. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *New England Journal of Medicine* 2017 doi: 10.1056/NEJMoa1703643 36. Vaidya JS, Massarut S, Vaidya HJ, et al. Rethinking neoadjuvant chemotherapy for breast cancer. *BMJ*	

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				2018;360:j5913. doi: 10.1136/bmj.j5913 [published Online First: 2018/01/13] 37. Cao Y, Willett WC, Rimm EB, et al. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. *BMJ* 2015;351:h4238. doi: 10.1136/bmj.h4238 [published Online First: 2015/08/20] 38. Kispert SE, Marentette JO, McHowat J. Enhanced breast cancer cell adherence to the lung endothelium via PAF acetylhydrolase inhibition: a potential mechanism for enhanced metastasis in smokers. *Am J Physiol Cell Physiol* 2014;307(10):C951-6. doi: 10.1152/ajpcell.00218.2014 [published Online First: 2014/09/05] 39. Kispert SE, McHowat J. Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. *Breast Cancer - Targets and Therapy* 2017;9:127-32. doi: 10.2147/BCTT.S129746 40. Chlebowski RT, Aragaki AK, Anderson GL, et al. Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women's Health Initiative Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017;35(25):2919-26. doi: 10.1200/JCO.2016.72.0326 [published Online First: 2017/06/28]	
University College London	Draft	4	12, 13	1.1.2 Use of MRI has not been shown to improve outcomes for breast cancer patients. A large randomised trial (COMICE trial) found that MRI does not improve management. On the other hand, it does delay surgery and can lead to an unnecessary increase in mastectomy rates by up to 6 times [1-4].MRI will not improve surgical accuracy or reduce	Thank you for your comment and for sending this information. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at

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				re-operation rates even for lobular cancers [1 5]. MRI will not reduce local recurrence either for invasive cancer[6] or DCIS[7]. MRI will not reduce contralateral breast cancer (incidence is 6% with or without pre-op MRI at 8 year-follow up)[6] From a meta-analysis of randomised trials of partial breast irradiation which included over 4500 patients, none of which included pre-operative MRI in their protocol, it is clear that overall survival is better by avoiding whole breast radiotherapy[8] and the tumour foci which would have been detected by MRI did not progress clinically. Therefore, use of MRI should not continue for certain indications due to the clear randomised evidence of lack of benefit in these instances. Efforts to start a randomised trial for theoretically beneficial indications should be encouraged.	the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest or include the references that you have highlighted. However, we will inform the surveillance team (which monitors and reviews new evidence to determine whether a guideline should be updated) of this evidence for consideration in the next update.
University College London	Draft	5	4	1.1.3 This should say: 'consider performing ultrasound-guided needle…', rather than 'perform ultrasound-guided needle…'. This is because the value of axillary clearance when only 1 or 2 lymph nodes are involved has been challenged by a large randomised trial – the ACOSOG Z0011 trial.[9] Centres of Excellence around the world have abandoned sampling of pre-treatment axillary US guided sampling unless more than 2 nodes are found to be grossly abnormal.	Thank you for your comment. The proposal not to include the referral, diagnosis and preoperative assessment section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update we are not able to make the changes that you suggest or include the references that you have highlighted. However, we will inform the surveillance team of this evidence for consideration in the next update.
University College London	Draft	5	24, 25	1.3.2 This sentence needs to spell out the exact risks and benefits – otherwise it will only depend on the bias/prejudice of the clinician – Unfortunately, there is no randomised evidence comparing the two interventions (surgery vs no surgery for 0-2mm margin). Therefore, this sentence only dilutes the guidance 1.3.1	Thank you for your comment and for recognising that there is insufficient evidence in the group of people with tumour at greater than 0mm but less than 2mm from the margin. However, the two recommendations that you mention are in two different groups of people - at the margin (where a clear recommendation has been made) and within 2mm

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				(lines 18-20) and lines 21-25 on page 5 and 1-3 on page 6 should be deleted.	but not at the margin (where a decision has to be made after a consideration of an individual's risks and benefits). We do not therefore agree that these recommendations should be deleted.
University College London	Draft	6	6	1.3.3 This should say – treatment for…….. DCIS and invasive cancer.	Thank you for your comment. The committee agreed that recurrence rates after surgery for all types of early and locally advanced breast cancer should be audited, and have amended the recommendation so it is no longer specific to DCIS.
University College London	Draft	7	5-7	1.4.6 This statement (and 1.1.3 as it stands) appears to contradict the statements on lines 11-23 because pre-operative sampling cannot differentiate between isolated tumour cells, micrometastases or between 1-2 nodes and > 2 nodes involvement. Therefore, sampling should be performed and acted upon only when there is gross involvement of more than 2 nodes in the axilla.	Thank you for your comment. The population considered in 1.4.6 are those where an abnormality has been picked up on ultrasound-guided needle biopsy, and the population referred to in 1.4.7 to 1.4.10 are those who have had a normal ultrasound but an abnormality has been detected by a subsequent sentinel lymph node biopsy. To avoid confusion this has been clarified in the guideline with the inclusion of a sub-heading '...in people with a normal preoperative ultrasound-guided needle biopsy before recommendation 1.4.7.
University College London	Draft	8	2-5	1.5 Breast reconstruction is suggested to be routinely offered with an assumption that it may improve quality of life for women undergoing mastectomy[10]. Nonetheless, there is a complete lack of high-quality evidence supporting reconstructive practice[11 12]. The most important parameters to assess breast reconstruction should be cancer outcome and the patient's own satisfaction with the cosmetic outcome. In this regard, one should remember that all systemic reviews included the Cochrane review have found no difference in patient satisfaction whether they have immediate or delayed or no reconstruction.[13] Only a randomised trial comparing these three options can inform about the potential benefits and indeed harms that may come from the significant additional surgical trauma, complications, and	Thank you for your comment and for your review of some references in this area. The aim of the review was to determine whether immediate breast reconstruction is clinically and cost effective compared with delayed reconstruction in women who may need postmastectomy radiotherapy. , References 10, 11, 12, 15, 16, and 17 did not therefore meet the inclusion criteria for our review. The Cochrane review (13) was checked for relevant studies but not included in its entirety due to the comparisons with no reconstruction. Book chapters (14)were not included in the evidence review as they did not meet the protocol criteria. However, the recommendations on breast reconstruction have been amended to include a separate

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				cost associated reconstructive procedures. The potential for real harm in terms of worsening cancer outcome has been well documented particularly in the last year.[14] for both immediate and delayed reconstruction. New evidence is emerging that suggests these extensive surgical procedures at the time of surgical extirpation of cancer may not always be oncologically safe. For example, an important although non-randomized study comes from University of Ireland involving 229 patients[15]. These breast cancer patients underwent immediate breast reconstruction between 2004 and 2009 and the authors found that 23% of patients suffered a wound complication. This complication rate is very much higher than those who have only a mastectomy without reconstruction, which is usually less than 5%. Even more worrisome than the higher complication rate after immediate reconstruction was the observation that those patients who had complications had a significantly lower 5-year relapse-free survival (64%) compared with those without complications (89%), a large difference that could not be explained by any patient or tumour factors. The authors suggest that the increased inflammatory response incited by the wound complications may be detrimental to cancer survival[15]. Furthermore, a large Scandinavian collaborative group reported in Lancet Oncology, the first randomised trial of immediate vs. delayed reconstruction with implant + acellular dermal matrix[16], a highly commendable effort. This 142-patient trial had to be stopped early because the Data Monitoring Committee felt it was not safe to continue. When immediate reconstruction was performed, there were many more complications (46% of cases) and re-operations (37%) compared with delayed reconstruction	recommendation stating that no breast reconstruction may be the preferred option for some women. Further, the introduction in the full evidence report has been amended to state that reconstruction may improve the quality of life after mastectomy. The recommendations have also been modified to make it clear that both delayed and immediate reconstruction are viable options and both should be offered. To help discussions on the risks and benefits of both options, a preference sensitive decision point table has also been included, outlining some of the topics which should be included in the discussion and decision-making process.

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				(18% and 15%). So, the high complication rate in the Irish study was no means unique. A similar picture appears to arise in the delayed reconstruction setting in a case-controlled study[17] which compared 312 patients with delayed reconstruction performed in a University Hospital in Norway between 1977 and 2007 with 1341 matched controls and found a remarkable peak hazard of relapse 18 months after reconstruction, similar to that normally observed at a similar time after the primary surgery. The authors also found that, 'the more extensive reconstruction modalities DIEP/TRAM procedures give rise to a higher early peak in comparison with unilateral implant surgery'. Such a dose-response relationship is usually characteristic of a causal link. They concluded that 'reconstructive breast cancer surgery constitutes an independent stimulating event on the growth of micro-metastases leading to accelerated relapse rates.' These studies raise the real concern that increasing surgical trauma and peri-operative inflammatory response may be triggering the growth of metastatic disease. In conclusion, even though it may seem logical and kinder to recommend a change of practice which would offer immediate breast reconstruction to all women undergoing mastectomy, this cannot be justified. The reasons for this are as follows: a) there is no evidence that it is beneficial to patients, b) it has increased risk of complications, c) it could worsen cancer outcome (a disservice to the patient), and d) it is more expensive to the NHS. Of course, the option can be discussed with patients, and offered if they wish to have it once all these known pros and cons (eg. potentially psychologically better coping with having a	

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				mastectomy vs. absence of any breast sensation, higher number of procedures, higher risk of complications, a possibility of higher distant relapse rate, and no evidence of improvement in patient satisfaction) are fully discussed comprehensively with the patient. However, without evidence of benefit, and in face of evidence of harm, as well as obvious need to have higher NHS resource utilisation, a blanket recommendation to change practice cannot be justified.	
University College London	Draft	15	22-23	1.10.1 This section should include the information that smokers who are given EBRT face a substantially higher risk of lung cancer and heart disease. For example, at 30 years, smokers receiving EBRT for breast cancer face an absolute risk of 13.8% of dying from lung cancer, a 4.4% increase in risk compared with those not given radiotherapy[18]. Therefore, it would follow that depending on their age, life expectancy and absolute benefit in terms of local recurrence and potentially survival, smokers could have a higher risk of dying from lung cancer than because of breast cancer. Individualised estimates about this should be shared with patients before their initial local treatment is decided.	Thank you for your comment. The review question aimed to determine which populations could receive partial breast radiotherapy compared to whole breast radiotherapy and there was no evidence identified in the review which provided data on a subgroup of people who are smokers, so the committee were unable to make a specific recommendation on smoking. However, we agree that all people undergoing radiotherapy should be advised to stop smoking and a link to the NICE guideline on stop smoking interventions has been included in section 1.14 Lifestyle of the guideline. There are also separate recommendations about limiting the dose of radiotherapy to the heart and lung.
University College London	Draft	16	1-8	1.10.2 The option of intraoperative radiotherapy using Intrabeam should be included in this section, even though the current NICE recommendation (issued as recently as 31 Jan 2018) is restricted to those centres which have the equipment and expertise. This may be a limited recommendation, nevertheless an important one and many patients stand to benefit. Based on the results of the TARGIT-A trial and Intrabeam radiotherapy system for adjuvant treatment of early breast cancer Technology appraisal guidance [TA501] Published date: 31 January 2018	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal ((TA501) has now been included in the guideline.

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				https://www.nice.org.uk/guidance/ta501, the following should be added: "Suitable patients (women >=45 years old, with ER positive invasive ductal carcinoma <=3.5cm in diameter, which is unifocal on routine imaging (MRI not required), without obvious axillary lymph node involvement should be offered targeted intraoperative radiotherapy with Intrabeam during their primary operation to remove the cancer (wide local excision). At present such patients can be referred to the hospitals that have the equipment and expertise. Patients should be informed of the 5-year risk of local recurrence (TARGIT IORT 2.1% vs conventional whole breast radiotherapy 1.1%, difference not statistically significant) and local recurrence free survival (93.9% vs 92.5%); that breast cancer survival was unchanged, but deaths from other causes (heart attacks and other cancers) was significantly reduced (1.3% vs 4.4%)[19 20]. The reduced mortality seen in the TARGIT-A trial has been subsequently confirmed in two meta-analysis of targeted radiotherapy [8 21]. There are also improvements in breast related quality of life[22], social and environmental benefits [23], and it is less costly to the NHS [20 24]. Surely it would be perverse for these updated NICE guidelines to be published without reference to the recently published guidelines by NICE itself. Furthermore, patients now have every right to be informed about Intrabeam radiotherapy before their operation and where it is available.	
University College London	Draft	16	18-25	1.10.5 Omitting radiotherapy and relying only on the use endocrine therapy is problematic because compliance with endocrine therapy for 5 years cannot be predicted and a significant proportion of patients who are initially willing to take endocrine therapy are forced to stop it because of side effects. Then it is too late to give radiotherapy.	Thank you for your comment. The evidence for this question included people who were randomised to endocrine therapy for 5 years, and not necessarily those who completed 5 years of treatment, and thus the committee considered this data to be applicable to the real-world situation where people may stop taking their

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				Furthermore, omitting radiotherapy has been repeatedly shown in randomised trials to lead to higher local recurrence rate (compared with whole breast or partial breast radiotherapy) even in the most selected cases and this should be conveyed to patients. It is important to recognise that compliance with endocrine therapy for 5 years cannot be predicted and a significant proportion of patients who are initially willing to take endocrine therapy are forced to stop it because of side effects. Therefore, the option of partial breast irradiation such as intraoperative radiotherapy, which can be given during the lumpectomy procedure, should be offered, as it is does not involve any additional burden to the patient and patients are likely to prefer it, rather than not having any radiotherapy treatment at all.	endocrine therapy because of side-effects. The committee disagreed with the statement 'then it is too late to give radiotherapy' as radiotherapy could be used at a later stage. The higher recurrence rates seen when omitting radiotherapy are detailed in the recommendations and should form part of the discussion when considering if radiotherapy can be omitted for individual people. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline.
University College London	Draft	16	15-17	1.10.4 The following should be considered because leaving the current wording unchanged can only be misleading. Partial breast irradiation using external beam radiotherapy offers no practical benefit to patients as they have to still travel daily to the radiotherapy centre for 3 weeks [21 25] Multicatheter interstitial brachytherapy over 5 days requires patient to live with multiple wires inserted in the breast and cosmetic outcome of such treatment has not been reported. [26]. To the best of our knowledge this method is not in use in the UK. Partial breast irradiation with intraoperative radiotherapy as per point 7. Above, has several benefits to patients and is cost-saving to the NHS and has been recently recommended by NICE in centres that have the equipment and expertise. https://www.nice.org.uk/guidance/ta501, Therefore, NICE should recommend that all options of partial breast irradiation are discussed properly with patients, irrespective of their local availability, and they should be given the ability to choose which option they prefer. This choice needs to be	Thank you for your comment. This recommendation refers to external beam radiotherapy because the committee did not review the evidence for intra-operative radiotherapy, as this was subject to a separate Technology Appraisal at the time this guideline was being developed. A link to this published appraisal (TA501) has now been included in the guideline. However, the dose fractionation details have been removed as no specific evidence was reviewed to recommend this dose over alternative regimens. The recommendations are, however, made on the basis of the best clinical evidence and not patient convenience, although the committee recognise that this factor will be considered by people when choosing treatment. Further, references 21 and 25 were not included in the current review as they are not original research (letter and commentary). The recommendation to consider interstitial brachytherapy has been removed as the committee agreed that although it is effective it is unlikely to be

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				offered ***before*** their primary operation so that the option of IORT is still available. At the same time, patients should be informed of the well documented risks of EBRT i.e. ischaemic heart disease even within the first 5 years after surgery and deaths from other cancers such as lung cancer. [18 27-29 30], which could be potentially avoided by radiation targeted to only the tumour bed[8].	acceptable to the majority of people. We did not have any evidence of increased risk of ischaemic heart disease or lung cancer in the studies included in our review. References 18 and 27 were not relevant to this review as they compared radiotherapy and no radiotherapy, rather than partial and whole breast radiotherapy; references 28 and 29 were not considered due to study design (non-RCT) and 30 was a letter to an editor. Studies included in the meta-analysis (8) were included in our review where they were consistent with the review protocol.
University College London	Draft	17	1-7	1.10.6 The way these numbers are expressed is misleading because they are expressed as per year, whereas most clinicians are used to reading the cumulative values for 5 or 10 years. Therefore, they should be expressed as "Without radiotherapy, local recurrence occurs in about 7 per 100 women at 5 years and 10 women per 100 at 10 years compared with 1-2 women per 100 at 5 years and 2-3 women per 100 at 10 years with radiotherapy."	Thank you for your comment. The figures have been changed to cumulative values for 5 years as you have suggested.
University College London	Draft	17	5-7	1.10.6 This statement is contrary to facts that show that there is indeed an increase in side effects if whole breast radiotherapy is given (eg. heart attacks and other cancers)[18 27-29] which can be avoided if targeted radiotherapy is given[30] – leading to an improved survival with targeted radiotherapy[8]. Therefore this sentence should be omitted from here.	Thank you for your comment. The lack of increase in cardiac failure, myocardial infarction or secondary cancer is in the specific group of very low risk women specified in the previous recommendation where there was no evidence of increased risk, and the wording of this recommendation has been amended so that this is clearer. The recommendations to minimise the cardiac morbidity when treating left-sided tumours have been moved to the beginning of the radiotherapy section so it is more obvious that they refer to all the other recommendations in the radiotherapy section. References 18 and 27 were not relevant to this review as they compared radiotherapy and no radiotherapy, rather than partial and whole breast radiotherapy; references 28 and 29 were not considered

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					due to study design (non-RCT) and 30 was a letter to an editor. Studies included in the meta-analysis (8) were included in our review where they were consistent with the review protocol.
University College London	Draft	17	12-13	1.10.8 – Change to 'Use a radiotherapy technique that minimises the dose to the lung and heart, including intraoperative radiotherapy.	Thank you for your comment. The committee did not review the evidence for intra-operative radiotherapy as this was subject to a separate Technology Appraisal at the time this guideline was being developed, so are unable to add this into this recommendation. However, a link to this published appraisal (TA501) has now been included in the guideline.
University College London	Draft	18	9	1.10.14 – Include – discuss participation in the HTA, NIHR funded TARGIT-B trial comparing intraoperative tumour bed boost with external beam radiotherapy boost, and testing if the former is superior.	Thank you for your comment. The proposal not to include the breast boost following breast-conserving surgery section of the guideline in this update was consulted on with registered stakeholders at the time of consultation on the draft scope. As this section was not included in the update only minor wording changes to the recommendation can be made and we are not able to make changes that alter the meaning. However, there is a new recommendation in the updated guideline on supporting entry into clinical trials for people with breast cancer.
University College London	Draft	19	10-18	This should be replaced by "Neoadjuvant chemotherapy should preferably be used in the setting of a controlled clinical trial If neoadjuvant chemotherapy is being used outside a clinical trial, patients should be informed that there is a 50-80% chance that there will be residual tumour in the breast or axilla at the end of neoadjuvant chemotherapy, that there is an increased risk of local recurrence and no benefit in terms of survival. Patients need to be informed that neoadjuvant chemotherapy is unlikely to benefit patients in over 90% of cases.	Thank you for your comment. The evidence reviewed by the committee showed that while there was an increase in local recurrence (from 9 to 12% for those that had neoadjuvant chemotherapy), the difference was not statistically significant; and there was no survival benefit, but this was not expected. There was benefit of reducing tumour size (11-83% response rate and 4-23% complete

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				Neoadjuvant chemotherapy does not improve survival and increases local recurrence.[31] After neoadjuvant chemotherapy, there may be an apparent reduction in size, but in reality, an improvement in breast preservation rate occurs in no more than 10% of patients; worse still, when the tumour size is 3cm or less, there is an increased risk of mastectomy.[32] Furthermore, neoadjuvant chemotherapy has been shown to increase the potential for metastatic dissemination[33] and based on the evolutionary model of cancer could lead to a higher risk of cancer cell clones resistant to chemotherapy.[34]" The NICE guidance on neoadjuvant chemotherapy with pertuzumab was published with an assumption that it might improve survival. However, now it is clear that there is no benefit to patients by the use of pertuzumab and addition of pertuzumab even in adjuvant setting does not improve overall survival[35] Important note: A rethink on the use of neoadjuvant chemotherapy has been suggested[36], which has resulted in spirited discussion amongst experts: the general consensus was that it does not improve overall survival and increases local recurrence http://www.bmj.com/content/360/bmj.j5913/rapid-responses	response) and a 15% difference in breast conservation rate with neoadjuvant chemotherapy. Thank you for the references you supplied. They did not meet the inclusion criteria for our review for the following reasons: references 31 and 36 were published after the cut-off date of our search; reference 32 is not a randomised controlled trial; reference 33 is an animal study; reference 34 is a commentary; and reference 35 did not compare neoadjuvant chemotherapy with no neoadjuvant chemotherapy. The committee considered that neoadjuvant treatment was now part of standard clinical practice, and therefore did not agree with the comment that it should only be considered within the setting of a clinical trial.
University College London	Draft	19, 21		This section gives no guidance about breast conserving surgery after neoadjuvant chemotherapy – As such whenever the extent of surgery is reduced because of neoadjuvant chemotherapy, there is an increase in local recurrence (by 3 -13%) and patients should be informed about this. [31]	Thank you for your comment. The committee did not consider evidence for breast-conserving surgery after neoadjuvant chemotherapy so were unable to make any recommendations relating to this.

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University College London	Draft	20	4-12	Neoadjuvant endocrine therapy – The formal randomised comparisons of primary endocrine therapy vs postoperative endocrine therapy have consistently shown a detrimental effect of breast cancer outcomes. 8Using neoadjuvant endocrine therapy to reduce the size of the tumour has never been tested in randomised trials. The only rationale for short term use of pre-operative endocrine therapy is for practical reason, while awaiting surgical treatment.	Thank you for your comment. There was only one study in our evidence review that compared neoadjuvant endocrine therapy with no neoadjuvant therapy, which showed no detrimental effect on overall survival. The committee reviewed evidence from randomised controlled trials that showed neoadjuvant endocrine therapy is as effective as neoadjuvant chemotherapy (which has a greater evidence base) at reducing tumour size in postmenopausal women, and so were able to recommend its use in this specific group, but made an additional recommendation to ensure that the risks and benefits for individual women were considered and discussed.
University College London	Draft	24	24-25	1.14.2. Patients should be informed that alcohol intake at any level increases the risk of development of new breast cancer and recurrence of breast cancer. The effect is linear and there is no threshold[37] Also, smoking increases the risk of breast cancer and its relapse, particularly in the lung [38 39]; also smoking would increase the risk of side effects of radiotherapy (esp. heart attacks and lung cancers) [18] Recommendation to patients should be to stop smoking. Furthermore, a long term diet that reduces fat content to less than 20%, and increases consumption of fruits, vegetables and grains reduces the risk of death after breast cancer. [40]	Thank you for your comment. The evidence review for this question focussed on the impact of lifestyle factors on recurrence, not the development of new breast cancer (37, 39), side effects of radiotherapy (18) or mortality (40) and the evidence available to the committee demonstrated a reduction in disease-free survival above a defined thresh-hold of alcohol intake, thus the recommendation has been phrased in this way. The evidence available to the committee did not demonstrate any effects of smoking on disease-free or overall survival and hence the committee were unable to include a recommendation on this. We did not include evidence from in-vitro studies (38) in the evidence review. The impact of fat intake was included in the evidence available to the committee and is discussed in the rationale and evidence report. However, no specific evidence on fruit, vegetable or grain consumption was available to the committee so they were unable to make recommendations on this.

Registered stakeholders

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