FINAL PROTOCOL

NHS REC No 04/MRE06/17

FAST

Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control

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TRIAL SUMMARY

Title	Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control.
Aim	To test 5 fractions of 5.7 Gy and 6.0 Gy against 25 fractions of 2.0 Gy in terms of late normal tissue effects and tumour control in women prescribed whole breast radiotherapy (no boost) after local excision of early breast cancer.
Eligibility criteria	***Inclusion criteria*** i) Age ≥ 50 years ii) Invasive carcinoma breast iii) Breast preserving surgery iv) Pathological tumour size < 3.0 cm v) Complete microscopic resection vi) Axillary node negative *Exclusion criteria* i) Mastectomy ii) Lymphatic radiotherapy iii) Radiotherapy breast boost iv) Neoadjuvant or adjuvant cytotoxic therapy
Study design	Prospective randomised controlled clinical trial.
Randomisation	Control arm: 50.0 Gy in 25 fractions of 2.0 Gy over 35 days Test arm 1: 30.0 Gy in 5 fractions of 6.0 Gy over 35 days Test arm 2: 28.5 Gy in 5 fractions of 5.7 Gy over 35 days
Radiotherapy delivery	Tangential fields to the whole breast; no boost; dosimetry must conform to ICRU 50/62 (+7%, -5%), no cardiac exposure.
Endpoints	*Primary* Change in photographic breast appearance. *Secondary endpoint* Tumour recurrence in the breast.

To randomise a patient please telephone the Trials Office
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1. TITLE

Prospective randomised clinical trial testing 5.7 Gy and 6 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control.

2. BACKGROUND

Human tumour responses are assumed to be insensitive to fraction size relative to dose-limiting late reacting normal tissues, a view that is consistent with the responses of animal tumours and human squamous carcinomas of the cervix uteri, lung and head and neck [12; 13; 17]. This means that as fraction size increases above 2.0 Gy, the gradient of the dose response curve is shallower for tumours than for late reacting normal tissues, a relationship highly unfavourable to cure. This relationship may not apply to all tumour types, though. An α/β value in the range 4 - 5 Gy was first estimated for the response of locally advanced and recurrent chest wall disease in the early 1950's and analysed using the linear quadratic model in the mid-1980's [3; 5]. More recently, a direct estimate of 4.1 Gy (95% CI 1.0 – 9.7) was reported for the fractionation sensitivity of breast cancer in The Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) Breast Fractionation Trial involving 1,410 patients [10]. If the high fractionation sensitivity of breast cancer is confirmed by the recent NCRI Standardisation of Radiotherapy (START) trial, the implications are that larger fraction sizes have no disadvantages, and perhaps have significant advantages, for women with early breast cancer.

Five fractions of 5.7 or 6.0 Gy are predicted by the linear quadratic model to be equivalent to 25 fractions of 2.0 Gy, assuming α/β values of 3.0 Gy and 4.0 Gy, for late normal tissue responses and tumour control, respectively [7]. Based on human skin responses, the linear-quadratic model performs reliably over this range of radiation fraction sizes [14; 15]. However, there is limited human experience with once-weekly fractionation in the context of breast cancer radiotherapy. Six fractions of 6.5 Gy over 6 weeks to the whole breast or chest wall using tangential megavoltage fields were evaluated in a series of 84 patients followed up for 36 – 94 months at Guildford, UK [11]. Acute skin reactions were reportedly mild and only 1/36 patients treated to whole breast developed a severe delayed skin reaction. In a recent French study, 152 women were treated with 5 fractions of 6.5 Gy over 5 weeks with 3 local relapses at a median follow up of > 5 years, but no comments on normal tissue responses [4]. Beside this, a number of UK and French clinical oncologists describe using once-weekly fractions of 6.0 – 6.5 Gy for breast radiotherapy in selected subgroups, typically the elderly or infirm, with favourable anecdotal impressions with respect to long-term safety and efficacy (*Yarnold, pers comm*). Although the existing data are encouraging and consistent with the predictions of empirical models, a randomised clinical trial is needed to formally test the safety of this approach prior to evaluating efficacy (tumour control) in a large national trial.

The economic impact of hypofractionation is relatively simple to estimate. Where health services resource usage is concerned, the costs of radiotherapy planning and of each fraction delivered are unaffected, but the costs of treatment delivery are reduced pro rata. Depending on the number of fractions delivered as part of current standard practice, radiotherapy workloads and costs would be dramatically reduced. At centres using standard regimens of 25 fractions, for example, the breast cancer workload on linear accelerators would fall by 80%. Since breast cancer accounts for 30% of UK

linear accelerator resource usage, the number of radiotherapy fractions delivered in UK radiotherapy departments would fall by up to 25%. There would also be major economic benefits for patients in terms of reduced hospital attendances.

Hypofractionation lends itself to acceleration, taking advantage of the relative sparing of early skin reactions as fraction size increases and the absence of a significant time dependency for late adverse effects. Tumour repopulation has recently been tested as a determinant of treatment outcome in the context of adjuvant systemic therapy. In a randomised comparison of conventional 3-weekly schedules of doxorubicin and cyclophosphamide with the same chemotherapy doses given at 2-weekly intervals (using growth factors to accelerate marrow recovery), the hazard ratios for disease-free and overall survival associated with 2-weekly chemotherapy were 0.74 ($p = 0.01$) and 0.69 ($p = 0.01$), respectively in 2,005 patients [2]. Recent reports of accelerated radiotherapy fractionation in head and neck cancer indicate that very modest shortening of treatment has a detectable impact on local control. In a trial of 1,476 patients randomised to 5 (control arm) or 6 (test arm) fractions per week of conventional radiotherapy, local tumour control in the test arm was 76% patients compared to 64% in the control group [9]. In this study, shortening treatment by only 7 days was associated with a 12% absolute reduction in local recurrence at the primary site, a reduction in the odds of recurrence of 16%. The implications for breast cancer are that modest reductions in treatment time may translate into worthwhile gains in tumour control without enhanced late normal tissue injuries. If the predicted late adverse effects of once-weekly 5.7 – 6.0 Gy fraction sizes are confirmed in the proposed FAST trial, it will encourage future evaluation of accelerated hypofractionated breast radiotherapy delivering 5 fractions over 1 – 2 weeks.

3. AIM

To test 5 fractions of 5.7 Gy and 6.0 Gy against 25 fractions of 2.0 Gy in terms of late normal tissue effects and tumour control in women prescribed whole breast radiotherapy (no boost) after local excision of early breast cancer.

4. ELIGIBILITY CRITERIA

Inclusion criteria

i) Age ≥ 50 years
ii) Invasive carcinoma breast
iii) Breast preserving surgery
iv) Pathological tumour size < 3.0 cm
v) Complete microscopic resection
vi) Axillary node negative

Exclusion criteria

i) Mastectomy
ii) Lymphatic radiotherapy
iii) Radiotherapy breast boost
iv) Neoadjuvant or adjuvant cytotoxic therapy.

5. RANDOMISATION

Control arm: 50.0 Gy in 25 fractions of 2.0 Gy over 35 days
Test arm 1: 30.0 Gy in 5 fractions of 6.0 Gy over 35 days
Test arm 2: 28.5 Gy in 5 fractions of 5.7 Gy over 35 days

The iso-effect relationships for these schedules are modelled in Appendix 1, based on the linear-quadratic model.

Entry procedure
Randomisation will be performed by telephone or facsimile to ICR-CTSU (web-based randomisation may become available during the life of the trial). Treatment allocation will be 1:1:1 and will use computer-generated random permuted blocks. Randomisation will be stratified by centre.

6. RADIOTHERAPY

General
The requirements defined below are regarded as the minimum, and should be adopted by all participants. Patients requiring lymphatic radiotherapy or breast boost should not be included in the trial. Both tangential fields to the whole breast must be treated with every fraction.

Breaks in the treatment due to bank holidays or equipment failure will be recorded but should not lead to modification of the radiotherapy dose or fractionation.

Patient position
The patient must lie supine and her position must remain unchanged during planning, simulation and treatment. The patient may lie on an inclined plane. Some form of immobilisation device, such as a breast board, is highly recommended. Reproducibility of the position should be verified by orthogonal laser beams.

Clinical target volume
Soft tissues of the whole breast down to the deep fascia, but not including underlying muscle and ribcage, nor overlying skin and excision scar.

Planning target volume
Entire breast with 1 cm margin to palpable breast tissue.

Medial and lateral borders should not normally extend beyond the anterior midline or the mid-axilla. It is desirable to reduce these margins in selected patients, if the tumour bed does not encroach, in order to reduce the volume of heart and/or lung in the high dose zone. Irradiation of the ribcage below the inframammary fold is unnecessary unless the tumour bed encroaches on this margin or the lower border of the breast overlaps the inframammary fold.

Deep margin extends down to the deep fascia, but the treatment volume inevitably includes pectoralis major and ribcage.

Field arrangement
Transverse cross-section of the patient is taken through the centre of the planning target volume using computerised tomography if possible; otherwise, an external contour is acceptable.

The maximum thickness of lung included in the tangential field is 2.0 cm, defined by computed tomography or simulator. Alternative verification of lung depth by machine films is acceptable. The anterior border of the field in free air should be at least 1 cm from the skin surface.

Cardiac shielding will be introduced using MLC or other shielding techniques.

Dose homogeneity & reference point
It is strongly recommended that the dose distribution across the target volume be modified to ensure a dose homogeneity within ICRU guidelines. If the maximum dose is > 107%, full dose compensation should be introduced where possible. Appendix 3 gives details of possible published methods and a description of a simple technique which may be adapted for either CT or multiple surface contour outlining.

Where full dose compensation is not technically possible, two further outlines are required in addition to the central contour; one at 1 cm inside the superior field border and one at 1 cm superior to the infra-mammary fold. These will give an indication of the likely maximum doses in the breast.

When calculating the dose distribution using a bulk density correction, the value used must be clearly stated.

Doses must be prescribed to the reference point which is at or near the centre of the target volume (ICRU 50). The point is half way between the lung surface and the skin surface on the perpendicular bisector of the posterior beam edge. Maximum and minimum doses must also be stated to describe dose homogeneity and the difference between these should be no more than 10% on the central plane and within ICRU guidelines over the whole breast where this data is available. Maximum doses in the superior plane and plane through the infra-mammary fold should be stated if full dose compensation is not used and only three outlines acquired.

Radiotherapy equipment
Megavoltage photons must be used. 4 - 6 MV photons are suitable for most patients. Tangential fields with large baseline separations may be best encompassed with 8 - 10 MV photons. Cobalt gamma-rays are not suitable.

7. FOLLOW-UP

A Case Report Form (CRF) booklet for each patient will be sent to the clinician after randomisation. The follow-up forms must be completed annually for 10 years (minimum 5 years).

8. ENDPOINTS

Primary endpoint
Change in photographic breast appearance.

Secondary endpoint
Tumour recurrence in the breast.

8.1 Assessments of endpoints

Primary endpoint: Photographic assessments of late adverse effects
Photographic assessments after breast conserving surgery will be taken at baseline, and at years 2 and 5. Timing of assessments is based on experience from the START trial, with the aim of maximising the information collected whilst minimising the assessment burden. Two frontal views of the chest will be taken, one with hands on the hips and the other with hands raised as far as possible above the head. Both photographs will exclude the head. Digital images (as for IMPORT) are acceptable.

Change of breast appearance compared with the post-surgical baseline will be scored on a three-point graded scale together with an assessment of breast size and surgical deficit. All photographs will be taken and stored locally in the first instance. Periodically, all photographs will be collected and assessed blind by a select group of observers. Reliability and repeatability of the assessments will be verified. The feasibility of and procedures for this scoring mechanism have been established in the START trial and assessment will continue using existing criteria.

Secondary endpoint: Tumour recurrence in the breast
Tumour relapse and new ipsilateral primary tumour must be confirmed by pathological assessment. Metastases will be determined by an appropriate combination of clinical, haematological, imaging and pathological assessment, recognising that pathological confirmation is not always possible.

Local tumour recurrence / ipsilateral new primary tumour defined as:
i) Breast parenchyma / skin within whole breast volume.

The following events will be recorded, but do not constitute secondary endpoints:
i) Regional metastases (axilla, supraclavicular fossa, internal mammary chain).
ii) Haematogenous metastases (only details of the first relapse are required).
iii) Death.

9. ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Sample size

The proportion of women recording any late change in breast appearance will be compared between trial arms. Assuming a α/β value of 3.5 Gy (average of 3.0 and 4.0 Gy for late effects), the two test regimens correspond to the delivery of 48 Gy and 52 Gy, respectively, in 2.0 Gy equivalents. Assuming the same α/β value, the two test schedules tested in the RMH/GOC Breast Fractionation Trial (39 Gy and 42.9 Gy in 13 fractions) are equivalent to 46 Gy and 53 Gy in 2.0 Gy equivalents. These two dose levels were associated with 13% and 28% rates, respectively, of change in breast appearance at 24 months. Assuming an average of 20% of women develop an

observable change in breast appearance 24 months after the proposed test arms, randomisation of 900 patients (300 per treatment arm) will allow an absolute 10% difference in the probability of a change in breast appearance between the two test dose levels to be detected with 90% power at the 5% significance level (2-sided test). Assuming linearity between the two dose levels of the test arms, the analysis would also allow interpolation (and limited degrees of projection or extrapolation if necessary) to determine the experimental schedule equivalent to daily fractions of 2.0 Gy. The estimate of sample size allows for 10% loss to follow-up.

9.2 Analysis

The principal analysis (late radiation effects on normal tissues and tumour recurrence) will be a logrank comparison of time from randomisation to the endpoint of interest by allocated treatment for all randomised patients (i.e. intention to treat). Incidence of late normal tissue effects will be analysed at two (primary analysis) and five years. For tumour recurrence, the primary endpoint is at five years. Survival analyses will assume that relapses before and after five years will be included in the analysis accordingly (i.e. patients will be followed from randomisation until it becomes impractical to do so further, and patients will only be censored in the analysis upon death or if lost to follow-up).

Analyses will compare fractionation schedules and will estimate the size of treatment effect with a confidence interval for the estimated difference between schedules. Information will be provided on both the absolute and relative treatment effect.

The incidence of uncommon complications will be monitored.

9.3 Interim analyses and data monitoring

Interim analyses of local tumour control, normal tissue responses, radiotherapy side-effects and the other endpoints will be conducted at yearly intervals and presented to an independent Data Monitoring and Ethics Committee (DMEC) for confidential review. In the light of the interim analyses, the DMEC will advise the Steering Committee if, in their view, the trial has indicated “proof beyond reasonable doubt” that one of the schedules is clearly indicated or contraindicated in terms of late radiation effects. In reviewing the evidence, the DMEC will also consider any available data from other randomised trials involving similar comparisons. The Steering Committee may then consider modification or termination of the study. Unless such a situation arises, the Steering Committee, the Trial Management Group, the collaborators and the central administrative staff (except the statistician who prepares the analyses) will remain unaware of the interim results. The DMEC may recommend continuation beyond the planned number of patients in the trial if it is felt that further information is required to address reliably the hypothesis in question.

9.4 Publication & Presentation

The success of the trial depends entirely on the participation by a large group of clinical oncologists. The main results of the trial will therefore be published in the name of the trial on behalf of all collaborators. All participants will be listed under the name of their hospital, together with the total number of patients entered.

10. ETHICS COMMITTEE APPROVAL

This trial has been approved by South West Multi-Centre Research Ethics Committee (NHS REC No 04/MRE06/17). Participants will also need the approval of their Local Research Ethics Committee. See Appendix 2 for patient information sheets, general practitioner information letter and patient consent forms.

11. PATIENT INFORMATION

The importance of providing a high level of information to patients is recognised. Patients will be informed of the services offered by cancerbackup in the trial information leaflets. The publications we aim to provide include Clinical Trials (booklet prepared by The Royal Marsden NHS Foundation Trust) and Breast Cancer (booklet prepared by cancerbackup). Local leaflets on radiotherapy should also be provided, but these must be approved by the appropriate committees before distribution. Each patient invited into the trial will receive an information sheet explaining the study in detail. In addition, the long-term side effects of radiotherapy to the breast area and the likelihood of these developing post treatment will be explained. We will ask for your permission to inform your GP about the study and your participation in it.

12. ASSOCIATED SUB-STUDIES

12.1 Molecular correlates of normal tissue injury

It is thought that part of the inter-patient variation in the incidence and severity of late normal tissue responses to radiotherapy reflect inter-patient differences in the expression of specific proteins (growth factors, extracellular matrix components etc). Common DNA sequence variations (single nucleotide polymorphisms) within the controlling regions or coding sequences of genes account for differences in protein expression between individuals that may explain an important component of the variation between individuals in late normal tissue responses to radiotherapy. Genome-wide approaches offer scope to identify patterns of single nucleotide polymorphisms that distinguish patients at lower and higher than average annual risk of late adverse effects. These genome wide approaches can be carried out on genomic DNA extracted from whole blood.

One sample of whole blood (up to 20mls) will be collected by venesection into blood tubes at the next annual follow up visit at the hospital. The sample will be sent to the Cancer Research UK/MRC Tissue Bank at Ninewells Hospital, Dundee, where it will be stored for future research having been separated into plasma and lymphocytes. The research may be carried out at another centre.

Patients will be asked to complete a family history questionnaire at the time of the blood sample donation. The questionnaire records cancer incidence in the patient's immediate family.

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APPENDIX 1

Iso-effect relationships for treatment schedules

Total doses delivered in 2.0 Gy equivalents (fractions) assuming different values of α/β are as follows (C = Control; T1 = Test arm1; T2 = Test arm 2):

Regimen (Gy / fractions)	Total dose in 2.0 Gy equivalents / 5 weeks				
	α/β = 2 Gy	α/β = 3 Gy	α/β = 3.5 Gy	α/β = 4 Gy	α/β = 10 Gy
C: 50.0 / 25	50.0	50.0	50.0	50.0	50.0
T1: 30.0 / 5	60.0	54.0	51.8	**50.0**	40.0
T2: 28.5 / 5	54.8	**49.6**	47.6	46.1	37.3

If the α/β value for tumour control is 10 Gy rather than 4 Gy, a clinically significant loss of tumour control would be expected. Based on results of the EORTC trial evaluating boost therapy, a dose reduction of 16 Gy in 2.0 Gy fractions would lead to an increase in local recurrence rate of 41% compared to Control [1]. Assuming linearity, the increase in local recurrence in Test arm 2 compared to Control would be approximately 33%. If the rate of local recurrence in the control arm is as high as 6% at 5 years, the corresponding rates in Test arms 1 and 2 could be up to 8%. If a low risk group is defined with a 10-year local recurrence risk of 5%, the potential penalty would be minimised. In the EORTC trial, this low level of local tumour recurrence was reported in approximately 2,400 women over 40 years of age allocated 50 Gy in 25 fractions to the whole breast without a boost [1].

APPENDIX 2

Version 4a, 8th August 2006

FAST Trial

Faster radiotherapy for breast cancer patients

Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy doses of whole breast radiotherapy in terms of i) adverse effects of radiotherapy on normal breast tissue which emerge at a later date and ii) tumour control

Patient information sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, including your GP, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Your doctor has advised you to have a course of radiotherapy as part of your treatment for breast cancer. Radiotherapy uses high-energy light waves called x-rays that have been used for many years to treat cancer patients. We know that cancer cells are sometimes left at the site of operation after removal of early breast cancer, despite the fact that the surgeon includes a margin of healthy tissue around the tumour and the pathologist sees no cancer cells at the edges of the surgical specimen. Radiotherapy is used to destroy any cancer cells left at the site of operation, even though we have no evidence that any cells remain in your case.

Standard schedules of radiotherapy were developed many decades ago. They deliver small doses (called fractions) of radiotherapy. Treatment regimens vary across the country. The standard treatment at this hospital is to have radiotherapy for 5 days per week for 3 weeks, 15 doses in all over a period of 21 days. Small doses are gentler than larger doses in their effects on normal tissues, but a large clinical trial has recently suggested that small doses are gentle on cancer cells as well. We think that a more effective approach to treatment may be to increase the size of individual doses and reduce the overall dose that is delivered, and this study has been designed to test the safety of this approach. We record the dose of radiotherapy in units of measurement called ‘gray’ (after a famous British scientist called Gray). So, instead of giving 15 doses of 2.67 gray (total dose 40 gray), we aim to test the effects of two new schedules: i) 5 doses of 6 gray (total dose 30 gray) and ii) 5 doses of 5.7 gray (total dose 28.5 gray) compared with a standard regimen of 25 doses of 2 gray (total dose 50 gray).

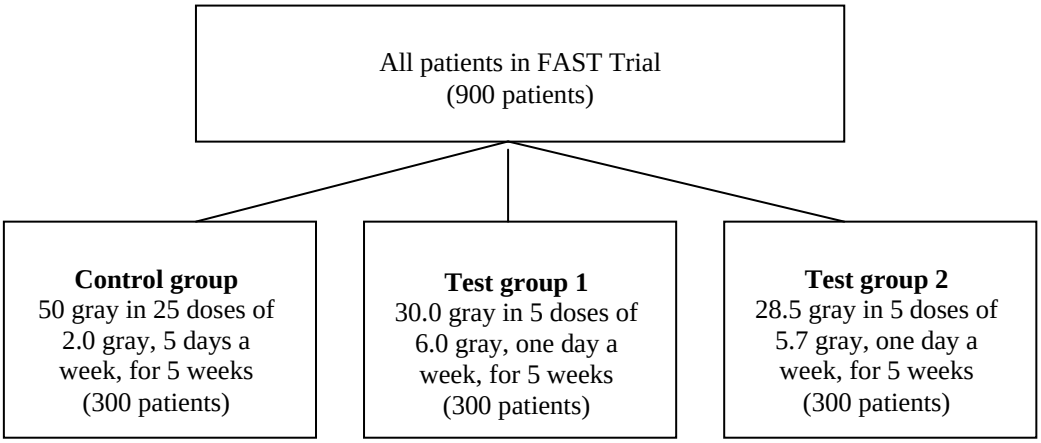
Why am I being invited to take part?
The group of women to be tested in this study is those who have average or below average risk of local tumour recurrence and who fulfil the following criteria:
To be *suitable* for this study:
i) You should be at least 50 years old.
ii) You should be diagnosed with invasive cancer of the breast.
iii) You should have had breast conserving surgery (not mastectomy).
iv) The tumour you had removed should be less than 3 cm in diameter.
v) The tumour should have been completely removed.
vi) You should have had lymph glands removed from your armpit (axilla) and all of these should be free of cancer cells.
You are *not suitable* for this study:
i) If you have had a mastectomy (removal of the breast).
ii) If you require radiotherapy to your armpit (axilla).
iii) If you require a breast boost to the area where your tumour was as part of your radiotherapy.
iv) If you have had chemotherapy.

Your doctor has checked your suitability for this research carefully, and we are inviting you to take part because we feel that you could benefit from the schedules we are testing. We plan to recruit a total of 900 women from a number of hospitals in the UK over a period of 30 months.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. A copy may also be sent to your trials office. You will be given a copy of the consent form to keep, together with this information sheet. We will ask for your permission to inform your GP about the study and your participation in it.

If you agree to join you are still free to withdraw at any time without giving a reason. If you withdraw from the study this will not affect the standard of care you receive. However, if this were to happen, we would like permission for your hospital to send information on your progress to the trials office in the Section of Clinical Trials at the Institute of Cancer Research who are co-ordinating the study. The information needed is routinely recorded in your medical records and you would not need to do anything. Collecting this information ensures that the overall quality of the research study is not impaired.

What will happen to me if I take part?
If you decide to take part in this trial, you will be allocated to one of the following treatment schedules:
Control group: 50.0 gray in 25 doses, 5 days a week for 5 weeks (standard radiotherapy dose).
Test group 1: 30.0 gray in 5 doses, 1 day a week for 5 weeks.
Test group 2: 28.5 gray in 5 doses, 1 day a week for 5 weeks.



The treatment you are allocated will be decided by a process called randomisation, and not chosen by you or your doctor. Randomisation is performed using a computer and allocates treatment rather like the toss of a coin. Randomisation is the only way that we obtain unbiased and trustworthy results.

Before you start your radiotherapy, we will ask you to attend the hospital for an appointment in the radiotherapy planning department. At this visit your radiotherapy will be planned. Detailed information about the area of your breast due to be treated will be entered onto a computer, and this information will be used to deliver your radiotherapy accurately and safely. The planning normally takes between 30 and 60 minutes.

Depending on which treatment you are allocated, you will then attend the hospital for radiotherapy either once a week or five times a week for five weeks. Each treatment session normally takes 10-15 minutes.

You will be asked to have a photograph of your breast taken before you start your radiotherapy and when you attend for follow-up appointments 2 years and 5 years after you finish your treatment. The photographs will help us assess any changes that may happen to your treated breast over a period of years. Only authorised researchers will have access to the photographs, which will be coded and stored in a safe manner at the Institute of Cancer Research.

What are the alternatives for treatment?
If you choose not to participate in this trial, you will be given radiotherapy treatment according to the current standard practice of your cancer centre.

What are the possible side effects?
As well as benefits, there are side effects associated with all radiotherapy schedules. During your radiotherapy treatment, you may experience a skin reaction, confined to the area being

treated. It will start about two weeks in to treatment, reaching a peak at the end, or within a week of finishing. The severity varies from person to person, but you may experience: dryness, reddening, itching/irritation, slight swelling or tenderness, increased pigmentation, like a suntan, skin breakdown, in areas of friction e.g. under the breast. If any of these skin reactions need medical attention, the radiographers will refer you to a specialist nurse in the department.

Long-term side effects in the breast area may develop many years after treatment and are usually permanent. Mild effects are common but don't usually interfere with everyday activities or lifestyle. A small proportion (less than 10%) of women develops more marked effects, which may interfere with some aspects of everyday life. These include change in the appearance of the skin, shrinkage of the breast, firmness of the breast, breast pain and tenderness, damage to lung tissue (less than 5%), damage to the bones (less than 5%) and damage of the heart tissue (left sided breast cancer only, less than 1%). We do not expect that these side effects will be any higher after the test schedules than after the schedule used in the Control arm.

What are the possible disadvantages and risks of taking part?
About 5 women per 100 treated develop marked breast shrinkage and/or discomfort several years after current standard radiotherapy. We do not expect the test schedules to be any different, but if we are wrong, this number could rise to 6 or 7 women per 100. We do not expect any reduction in the effectiveness of the treatment against cancer recurrence in the breast, although this will take several thousand research volunteers to demonstrate. If the new treatment is less effective than standard treatment in eradicating cancer cells in this respect, it is likely that this would affect, at worst, 1 patient out of every 100 treated.

What are the possible benefits of taking part?
There are practical benefits of a treatment that involves fewer visits to hospital. We think the treatment will cause the same level of early and late (years later) side effects as standard treatment, or even milder effects. Any cancer cells remaining in the breast are likely to be eradicated at least as effectively as current treatment.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What is the expense of volunteering?
None.

Will I be paid for taking part in this study?
No. Neither you nor your doctor will be paid for taking part.

Are there any restrictions on what I might eat or do?

If you are of childbearing age, it is important to avoid pregnancy whilst on treatment, so contraceptive measures must be used.

What if something goes wrong?
Your progress will be watched closely during and after treatments and you will be offered whatever treatment is available to help with any side effects. We do not believe you will suffer any injury from participating in this study. You should however know that if you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence then you have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated, the normal NHS complaints mechanism is open to you. Your hospital will have a formal complaints procedure that is available to you.

Will my taking part in this study be kept confidential?
Your medical records will need to be seen by authorised members of the research team at your hospital, so that they can collect information needed for this research study and also to check that it is correct. Your name, date of birth and NHS number will be passed to the trials office at the Institute of Cancer Research when you join the study so that they can find you again if you lose touch with your hospital in the future. You will be given a unique registration number, which will be used together with your initials and hospital number on forms that the research staff sends to the trials office. Information from your medical records about your treatment and disease will be sent to the trials office at the Institute of Cancer Research. Representatives from this organisation and/or regulatory bodies may wish to see your hospital or clinic records to make sure the information sent was correct. All information which is collected about you during the course of the research will be kept strictly confidential and nothing that might identify you will be revealed to any third party.

We will be contacting your hospital over the years to find out how you are getting on. Ideally we would like to do this for life, but patients often change address and/or GP or lose touch with their hospital. If this happens we would like to use national records which are kept on everyone's health status to find out how you are. One of these is held at the General Register Office (GRO). We will need to give them enough information to identify you. This is usually your name, date of birth and NHS number (or Community Health Index and/or hospital number in Scotland). Any details we receive from any source are confidential and will only be used for the purposes of the FAST trial. Please initial the consent form to show that we have your permission to do this.

GP notification
Your GP will be informed of your participation in the trial with your permission. If you withdraw from the study, we will ask your GP to provide authorised researchers with basic clinical information that would routinely be collected and written in your medical records.

What will happen to the results of the research study?
Independent experts will review the progress of the research, and the results will be published in a respected medical journal as soon as there is enough information to be sure the results are reliable. You will not be identified in any report or publication. The results will help to decide how best to deliver radiotherapy to patients with breast cancer in the future.
Your hospital will write to you when the results are known to ask if you would like to see them. The letter will explain how to get a copy.

Who is organising the study?
This research is being organised by Professor John Yarnold, Consultant Clinical Oncologist at the Royal Marsden Hospital in Sutton in collaboration with other cancer specialists at centres throughout the UK. The trials office co-ordinating the study is based in the Section of Clinical Trials at the Institute of Cancer Research, Sutton, Surrey.

If you are a private patient, please inform your insurance company that you are participating in this study, in order to ensure that your medical expenses will be covered. This applies to all research studies, not just this one.

Who has reviewed the study?
We have approval for the study from an NHS Research Ethics Committee and the local research ethics committees at the institutions involved in the research. All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

Contact for the Further Information
Local treatment centre details including trial personnel as well as availability of language line or other facility for translation.

Thank you very much for your help.

Date given to patient:_____

Version 4b, 8th August 2006

FAST Trial

Faster radiotherapy for breast cancer patients

Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy doses of whole breast radiotherapy in terms of i) adverse effects of radiotherapy on normal breast tissue which emerge at a later date and ii) tumour control

Patient information sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, including your GP, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Your doctor has advised you to have a course of radiotherapy as part of your treatment for breast cancer. Radiotherapy uses high-energy light waves called x-rays that have been used for many years to treat cancer patients. We know that cancer cells are sometimes left at the site of operation after removal of early breast cancer, despite the fact that the surgeon includes a margin of healthy tissue around the tumour and the pathologist sees no cancer cells at the edges of the surgical specimen. Radiotherapy is used to destroy any cancer cells left at the site of operation, even though we have no evidence that any cells remain in your case.

Standard schedules of radiotherapy were developed many decades ago. They deliver small doses (called fractions) of radiotherapy. Treatment regimens vary across the country. The standard treatment at this hospital is to have radiotherapy for 5 days per week for 5 weeks, 25 doses in all over a period of 35 days. Small doses are gentler than larger doses in their effects on normal tissues, but a large clinical trial has recently suggested that small doses are gentle on cancer cells as well. We think that a more effective approach to treatment may be to increase the size of individual doses and reduce the overall dose that is delivered, and this study has been designed to test the safety of this approach. We record the dose of radiotherapy in units of measurement called ‘gray’ (after a famous British scientist called Gray). So, instead of giving 25 doses of 2 gray (total dose 50 gray), we aim to test the effects of two new schedules: i) 5 doses of 6 gray (total dose 30 gray) and ii) 5 doses of 5.7 gray (total dose 28.5 gray).

Why am I being invited to take part?

The group of women to be tested in this study is those who have average or below average risk of local tumour recurrence and who fulfil the following criteria:

To be *suitable* for this study:

i) You should be at least 50 years old.
ii) You should be diagnosed with invasive cancer of the breast.
iii) You should have had breast conserving surgery (not mastectomy).
iv) The tumour you had removed should be less than 3 cm in diameter.
v) The tumour should have been completely removed.
vi) You should have had lymph glands removed from your armpit (axilla) and all of these should be free of cancer cells.

You are *not suitable* for this study:

i) If you have had a mastectomy (removal of the breast).
ii) If you require radiotherapy to your armpit (axilla).
iii) If you require a breast boost to the area where your tumour was as part of your radiotherapy.
iv) If you have had chemotherapy.

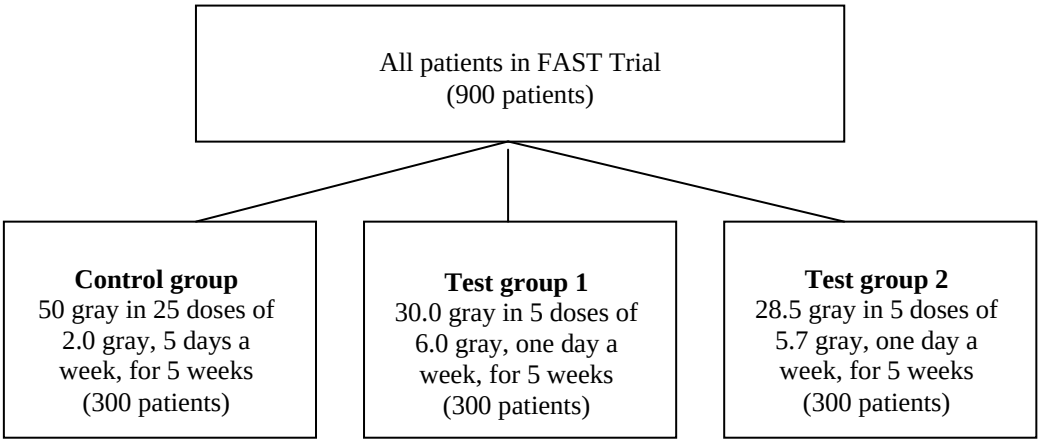
Your doctor has checked your suitability for this research carefully, and we are inviting you to take part because we feel that you could benefit from the schedules we are testing. We plan to recruit a total of 900 women from a number of hospitals in the UK over a period of 30 months.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. A copy may also be sent to your trials office. You will be given a copy of the consent form to keep, together with this information sheet. We will ask for your permission to inform your GP about the study and your participation in it.

If you agree to join you are still free to withdraw at any time without giving a reason. If you withdraw from the study this will not affect the standard of care you receive. However, if this were to happen, we would like permission for your hospital to send information on your progress to the trials office in the Section of Clinical Trials at the Institute of Cancer Research who are co-ordinating the study. The information needed is routinely recorded in your medical records and you would not need to do anything. Collecting this information ensures that the overall quality of the research study is not impaired.

What will happen to me if I take part?
If you decide to take part in this trial, you will be allocated to one of the following treatment schedules:
Control group: 50.0 gray in 25 doses, 5 days a week for 5 weeks (standard radiotherapy dose).
Test group 1: 30.0 gray in 5 doses, 1 day a week for 5 weeks.
Test group 2: 28.5 gray in 5 doses, 1 day a week for 5 weeks.



The treatment you are allocated will be decided by a process called randomisation, and not chosen by you or your doctor. Randomisation is performed using a computer and allocates treatment rather like the toss of a coin. Randomisation is the only way that we obtain unbiased and trustworthy results.

Before you start your radiotherapy, we will ask you to attend the hospital for an appointment in the radiotherapy planning department. At this visit your radiotherapy will be planned. Detailed information about the area of your breast due to be treated will be entered onto a computer, and this information will be used to deliver your radiotherapy accurately and safely. The planning normally takes between 30 and 60 minutes.

Depending on which treatment you are allocated, you will then attend the hospital for radiotherapy either once a week or five times a week for five weeks. Each treatment session normally takes 10-15 minutes.

You will be asked to have a photograph of your breast taken before you start your radiotherapy and when you attend for follow-up appointments 2 years and 5 years after you finish your treatment. The photographs will help us assess any changes that may happen to your treated breast over a period of years. Only authorised researchers will have access to the photographs, which will be coded and stored in a safe manner at the Institute of Cancer Research.

What are the alternatives for treatment?
If you choose not to participate in this trial, you will be given radiotherapy treatment according to the current standard practice of your cancer centre.

What are the possible side effects?
As well as benefits, there are side effects associated with all radiotherapy schedules. During your radiotherapy treatment, you may experience a skin reaction, confined to the area being

treated. It will start about two weeks in to treatment, reaching a peak at the end, or within a week of finishing. The severity varies from person to person, but you may experience: dryness, reddening, itching/irritation, slight swelling or tenderness, increased pigmentation, like a suntan, skin breakdown, in areas of friction e.g. under the breast. If any of these skin reactions need medical attention, the radiographers will refer you to a specialist nurse in the department.

Long-term side effects in the breast area may develop many years after treatment and are usually permanent. Mild effects are common but don't usually interfere with everyday activities or lifestyle. A small proportion (less than 10%) of women develops more marked effects, which may interfere with some aspects of everyday life. These include change in the appearance of the skin, shrinkage of the breast, firmness of the breast, breast pain and tenderness, damage to lung tissue (less than 5%), damage to the bones (less than 5%) and damage of the heart tissue (left sided breast cancer only, less than 1%). We do not expect that these side effects will be any higher after the test schedules than after the schedule used in the Control arm.

What are the possible disadvantages and risks of taking part?
About 5 women per 100 treated develop marked breast shrinkage and/or discomfort several years after current standard radiotherapy. We do not expect the test schedules to be any different, but if we are wrong, this number could rise to 6 or 7 women per 100. We do not expect any reduction in the effectiveness of the treatment against cancer recurrence in the breast, although this will take several thousand research volunteers to demonstrate. If the new treatment is less effective than standard treatment in eradicating cancer cells in this respect, it is likely that this would affect, at worst, 1 patient out of every 100 treated.

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Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What is the expense of volunteering?
None.

Will I be paid for taking part in this study?
No. Neither you nor your doctor will be paid for taking part.

Are there any restrictions on what I might eat or do?

If you are of childbearing age, it is important to avoid pregnancy whilst on treatment, so contraceptive measures must be used.

What if something goes wrong?
Your progress will be watched closely during and after treatments and you will be offered whatever treatment is available to help with any side effects. We do not believe you will suffer any injury from participating in this study. You should however know that if you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence then you have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated, the normal NHS complaints mechanism is open to you. Your hospital will have a formal complaints procedure that is available to you.

Will my taking part in this study be kept confidential?
Your medical records will need to be seen by authorised members of the research team at your hospital, so that they can collect information needed for this research study and also to check that it is correct. Your name, date of birth and NHS number will be passed to the trials office at the Institute of Cancer Research when you join the study so that they can find you again if you lose touch with your hospital in the future. You will be given a unique registration number, which will be used together with your initials and hospital number on forms that the research staff sends to the trials office. Information from your medical records about your treatment and disease will be sent to the trials office at the Institute of Cancer Research. Representatives from this organisation and/or regulatory bodies may wish to see your hospital or clinic records to make sure the information sent was correct. All information which is collected about you during the course of the research will be kept strictly confidential and nothing that might identify you will be revealed to any third party.

We will be contacting your hospital over the years to find out how you are getting on. Ideally we would like to do this for life, but patients often change address and/or GP or lose touch with their hospital. If this happens we would like to use national records which are kept on everyone's health status to find out how you are. One of these is held at the General Register Office (GRO). We will need to give them enough information to identify you. This is usually your name, date of birth and NHS number (or Community Health Index and/or hospital number in Scotland). Any details we receive from any source are confidential and will only be used for the purposes of the FAST trial. Please initial the consent form to show that we have your permission to do this.

GP notification
Your GP will be informed of your participation in the trial with your permission. If you withdraw from the study, we will ask your GP to provide authorised researchers with basic clinical information that would routinely be collected and written in your medical records.

What will happen to the results of the research study?
Independent experts will review the progress of the research, and the results will be published in a respected medical journal as soon as there is enough information to be sure the results are reliable. You will not be identified in any report or publication. The results will help to decide how best to deliver radiotherapy to patients with breast cancer in the future.
Your hospital will write to you when the results are known to ask if you would like to see them. The letter will explain how to get a copy.

Who is organising the study?
This research is being organised by Professor John Yarnold, Consultant Clinical Oncologist at the Royal Marsden Hospital in Sutton in collaboration with other cancer specialists at centres throughout the UK. The trials office co-ordinating the study is based in the Section of Clinical Trials at the Institute of Cancer Research, Sutton, Surrey.

If you are a private patient, please inform your insurance company that you are participating in this study, in order to ensure that your medical expenses will be covered. This applies to all research studies, not just this one.

Who has reviewed the study?
We have approval for the study from an NHS Research Ethics Committee and the local research ethics committees at the institutions involved in the research. All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

Contact for the Further Information
Local treatment centre details including trial personnel as well as availability of language line or other facility for translation.

Thank you very much for your help.

Date given to patient:_____

MREC Study Number:
Patient ID Number: _____

Version 4a, 8th August 2006

CONSENT FORM

Title of Project: **FAST Trial - Faster radiotherapy for breast cancer patients**
Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy doses of whole breast radiotherapy in terms of i) adverse effects of radiotherapy on normal breast tissue which emerge at a later date and ii) tumour control

Chief Investigator: Professor John Yarnold, Consultant Clinical Oncologist

Please initial box

1. I confirm that I have read and understand the information sheet *Version 4a dated 8th August 2006* for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. If I withdraw from the study, I consent to my doctor providing authorised researchers with basic clinical information that would routinely be collected and written in my medical records. ☐
4. I understand that sections of my medical notes may be looked at by responsible individuals from the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I understand that data, as described in the Patient Information Sheet will be passed to the Section of Clinical Trials, Institute of Cancer Research. I understand my name will be given when I join the study, and that thereafter I will be identified by a unique trial number, initials and hospital number. Any information passed to the regulatory authorities will not identify me as an individual. ☐
6. I agree to have photographs taken of my breast after my operation and at intervals during my follow up. ☐
7. I agree to my GP being informed about my participation and treatment in this study. ☐
8. I consent to the Institute of Cancer Research using information held by the NHS and the General Register Office (GRO) as described in the Patient Information Sheet, if it becomes necessary to trace my health status. ☐
9. I agree to take part in this study. ☐
10. I give permission for a copy of my radiotherapy treatment plan and associated CT and treatment images to be monitored and stored by the national trials QA team. I understand that this data will be anonymised prior to storage and may be used for future research in patients treated with radiotherapy. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking Consent	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

MREC Study Number:
Patient ID Number: _____

Version 4b, 8th August 2006

CONSENT FORM

Title of Project: **FAST Trial - Faster radiotherapy for breast cancer patients**
Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy doses of whole breast radiotherapy in terms of i) adverse effects of radiotherapy on normal breast tissue which emerge at a later date and ii) tumour control

Chief Investigator: Professor John Yarnold, Consultant Clinical Oncologist

Please initial box

1. I confirm that I have read and understand the information sheet *Version 4b dated 8th August 2006* for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. If I withdraw from the study, I consent to my doctor providing authorised researchers with basic clinical information that would routinely be collected and written in my medical records. ☐
4. I understand that sections of my medical notes may be looked at by responsible individuals from the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I understand that data, as described in the Patient Information Sheet will be passed to the Section of Clinical Trials, Institute of Cancer Research. I understand my name will be given when I join the study, and that thereafter I will be identified by a unique trial number, initials and hospital number. Any information passed to the regulatory authorities will not identify me as an individual. ☐
6. I agree to have photographs taken of my breast after my operation and at intervals during my follow up. ☐
7. I agree to my GP being informed about my participation and treatment in this study. ☐
8. I consent to the Institute of Cancer Research using information held by the NHS and the General Register Office (GRO) as described in the Patient Information Sheet, if it becomes necessary to trace my health status. ☐
9. I agree to take part in this study. ☐
10. I give permission for a copy of my radiotherapy treatment plan and associated CT and treatment images to be monitored and stored by the national trials QA team. I understand that this data will be anonymised prior to storage and may be used for future research in patients treated with radiotherapy. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking Consent	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Version 2, June 2004

FAST Trial

Faster radiotherapy for breast cancer patients

Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy doses of whole breast radiotherapy in terms of i) adverse effects of radiotherapy on normal breast tissue which emerge at a later date and ii) tumour control

GP Letter

Dear Dr *name of GP*

Re: *name and date of birth of patient*

This patient of yours has been invited to participate in prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control. I enclose a copy of the patient information sheet given to the patient for your information. If you wish to have further details about this study, please do not hesitate to contact me at the above address.

Yours sincerely

Professor John Yarnold
Chief Investigator and Consultant in Charge

APPENDIX 3

A list of possible compensation methods is given in the Table.

Method	References	Comments
Physical compensators based on equivalent path length	Wilks *et al* [16]	Osiris system (QADOS) commercially available - would require the iso-dose planning module.
Simple manual segments	Kestin *et al* [8] Zachrisson *et al* [18]	Straightforward and can be achieved with CT or other outlining methods as long as the minimum slice set of 5 outlines is obtained.
Commercial planning systems plane compensation algorithms	Varian Cadplan MDS Nordion Helax Adac Pinnacle Nucleotron Plato/OPT	Available on many planning systems (combining with a wedge on one field may improve dosimetry further)
Inverse planning algorithms on commercial planning systems	Varian Cadplan/Helios Nucleotron OPT Adac Pinnacle	This is an alternative if the plans meet the ICRU 50 and 62 criteria
Electronic portal imaging	Evans *et al* [6]	Expertise exists and could be made available to implement this method with any portal imager with good dosimetric stability and accuracy.
Other techniques	As applicable	An alternative if the plans meet the ICRU 50 and 62 criteria

SUGGESTED SIMPLE METHOD FOR BREAST COMPENSATION USING 1-2 EXTRA MLC SEGMENTS

1. A simple manual design for one or two extra segments added to a good, tangential pair plan requires:
   - An outlining system where multiple slices may be efficiently gathered
   - A means of transferring these to a planning system with a beam eye view facility and a means of viewing a sagittal slice through the breast.

   (Although, a planning system with a facility to create multi-segments inside a beam is useful, the segments, as they are few, may be separate beams).

2. A sufficient number of transverse sections of the patient are required, either from CT or another valid outlining system e.g. Osiris (QADOS). It is recommended that there are no less than five slices and preferably more, spaced appropriately throughout the volume.

3. The slices are transferred to the planning system, and the geometry set up as for a standard wedged tangential pair. A PTV may be defined, however, using the 50% iso-dose for the patient contour as an indication of irradiated volume should be sufficient for plan analysis.

4. A good wedge only plan is produced.

5. A sagittal view through the breast is created with the appropriate iso-dose lines displayed. For some planning systems this may be overlaid in the BEV window; for others it may be necessary to transfer it to a transparency to use as a template for designing the fields. Where CT data exist then careful windowing of DRRs may allow segment design in the BEV.

6. Each medial and lateral beam is copied either to give a plan with four beams if the system allows multi-segments in a beam if there are two or more new segments; or copied to give a new beam for each segment. The new beams do not have a wedge, and may be oriented to optimise the direction of travel of the MLC leaves. The sagittal view/template/windowed DRR is used to bring in MLC leaves to cover e.g. the 105% iso-dose lines. If higher iso-dose lines e.g. 110% are seen, a second segment may be used in the same way to cover these.

7. The segments are weighted at 5 - 8% of the isocentric weight of the wedged fields.

8. The design is repeated for the other tangential field.

9. The plan is calculated and assessed. A small amount of iteration to the field shape and /or beam weight may be required to reduce the high dose volume to the level required.