



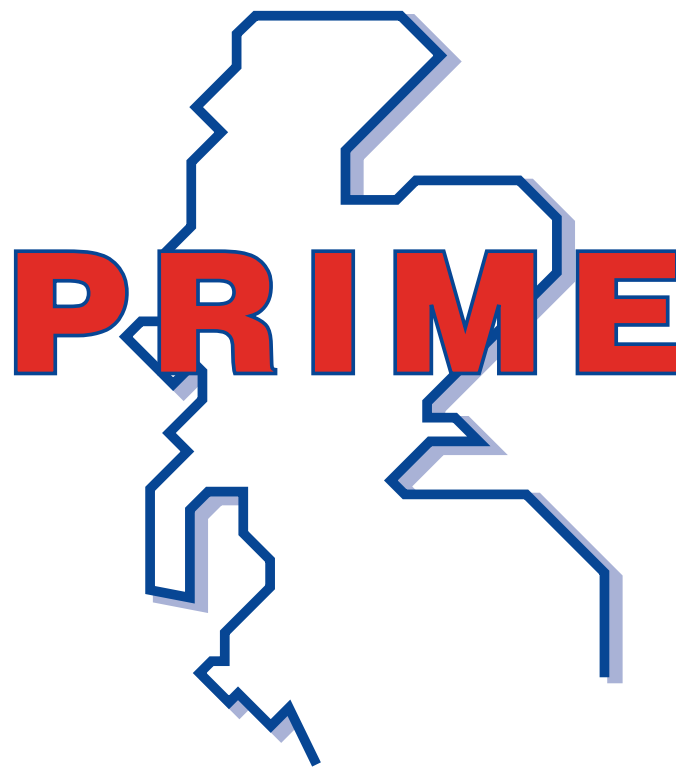
NHS Research & Development

The HTA programme

NCCHTA

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The **PRIME** Breast Cancer Trial



Protocol

(**P**OSTOPERATIVE **R**ADIOOTHERAPY **I**N
MINIMUM-RISK **E**LDERLY)

Under the auspices of the Scottish Breast Trials Group

Funded by the NHS Research and Development Health Technology
Assessment Programme

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Introduction

The PRIME Trial is a randomised controlled clinical trial to evaluate the quality of life and clinical cost-effectiveness of adjuvant irradiation for elderly breast cancer patients with early operable breast cancer. It was derived following a call from the NHS Research and Development Health Technology Assessment Programme on adjuvant therapies in the elderly with a main focus on quality of life and cost-effectiveness. The trial is funded for 5 years, actively recruiting for 3 of those years, with each patient being followed up by trial personnel for a minimum of 15 months. The clinical outcome in terms of recurrence and survival will be monitored on a long term basis in accordance with standard clinical practice.

1. Background

Just under half of all breast cancers occur in women aged 65 years and over with the peak incidence rate occurring in women in their ninth decade of life (Yancik et al 1989). In the period 1992 to 1995 there were 6,636 incident breast cancers (42% of all breast cancers) in this age group in Scottish women alone (Thomson 1997). This number is set to increase due to a rise in the age-specific incidence of the disease (Brody and Cassell 1990) and the demographic changes in the population (Haynes and Feinleib 1980). Additionally, if the invitation to breast cancer screening is extended beyond the current UK limit of 64 years, more elderly women may be diagnosed with breast cancer. In any case, there may also be an increase due to women currently below the age of 65 years wishing to continue with breast cancer screening.

In Scotland in 1993 44% of women aged 70 years or more with node negative breast cancer underwent breast conserving surgery (Stroner 1997). The standard adjuvant treatment regime for these women at present is Tamoxifen followed by irradiation of the breast with or without peripheral lymphatic irradiation. Much of the research that has been undertaken looking at different treatment modalities in breast cancer has been limited to younger women and has included outcome measures such as mortality which may be of less importance to older women. The literature clearly documents the independent benefit of adjuvant Tamoxifen in younger women (Early Breast Cancer Trialists' Collaborative Group 1992). This has not been reported in women over the age of 70 years. There is also a strong body of evidence supporting the use of adjuvant radiotherapy in younger women in terms of reducing recurrence rates (Recht et al 1988, Veronesi et al 1993). However the results from these studies may not be generalisable to older women. For example, older women with local or loco-regional disease may have less aggressive cancers (Kurtz 1992). A review of the literature revealed a dearth of research looking at the benefits of radiotherapy for early breast cancer in older women. Randomised trials which have assessed the benefits of breast irradiation have been predominantly carried out in women under the age of 70 and the outcome measures in these trials did not include quality of life or functional outcomes (Fisher et al 1995, Clark et al 1996, Forrest et al 1996). There is clearly a need therefore to establish whether radiotherapy is of benefit to older women using outcome measures which are relevant to them and also to establish the cost-effectiveness of such treatment from the NHS perspective. Demographic changes and the epidemiological trends for breast cancer coupled with the possible increasing importance of breast cancer screening in older women add impetus to the need for this research.

As radiotherapy has been shown to reduce the rates of local recurrence by up to four fold (Forrest et al 1996) any trial which intends to remove adjuvant radiotherapy must therefore select a study population which is at low risk of developing a recurrence (Recht et al 1988, Kurtz 1992). Recurrence rates tend to fall with increasing age (Veronesi et al 1993, Nemoto et al 1991). It is not clear, however, whether age is an independent risk factor for recurrence because younger women are more likely to have tumours with an extensive intraductal component, lympho-vascular invasion or high grade histology. Women with lymphatic/vascular invasion have a two fold increase of recurrence of their breast cancer relative to women who do not have this feature and high grade tumours confer a similar relative risk compared to lower grade tumours (Locker et al 1989, Kurtz 1992). The most important risk factor however for recurrence is the involvement of a resection margin which is associated with a nine fold increase in risk (Smitt et al 1995). Given this profile of risk factors it is therefore possible to select elderly breast cancer patients who would be at low risk of recurrence to establish whether radiotherapy conferred any benefit in their management. Additionally, as it is already known that recurrence rates following breast conserving therapy without radiotherapy in the elderly with early breast cancer are low (Veronesi et al 1993, Nemoto et al 1991, Gruenberger et al 1998), it would be ethical to conduct a randomised controlled trial to investigate the costs and benefits of radiotherapy in these patients. The preliminary analysis of the BASO II trial of grade I cancers or those of special type (Blamey 1999) shows a local recurrence rate of 5% (6/120) at a median follow-up of 48 months in the arm treated by wide local excision alone. The local recurrence rate in the wide local excision + radiotherapy group was 2.5% (3/121). Local recurrence rates in the arm treated by wide local excision and Tamoxifen, as in our proposed trial, are likely to be lower than 5% although these data are not yet published. The retrospective study of Gruenberger et al 1998 shows a 3% local recurrence rate at a median follow-up of 60 months in 'low risk' (node negative, oestrogen receptor positive) patients without irradiation. A similar group that received irradiation had a 2.6% local recurrence rate. The patients in this study were 60 years or older, treated by quadrantectomy and axillary node clearance. Although the extent of local surgery is greater than the wide local excision in the PRIME trial, the risks of local recurrence in our selected group of patients are low. A similar trend to lower recurrence rates in older patients is shown in the Milan trial (Veronesi et al 1993) which demonstrated a 3.8% local recurrence rate in women over 55, treated by quadrantectomy and axillary clearance, compared to 8.7% and 17.5% in the 46-55 and <45 age groups respectively.

Outcomes such as quality of life and functional status may be more important outcome measures than the length of survival in elderly patients, due to co-existing morbidity and the more limited life expectation of these patients relative to younger women. Complications such as breast pain, pneumonitis and rib fractures may prove more distressing for an elderly patient. Other factors such as the inconvenience of four to five weeks of extra inpatient/outpatient hospital treatment also need to be considered when appraising the benefits of radiotherapy for individual patients. These outcome measures have not been documented in a comprehensive way in older patients with breast cancer.

In addition to patient oriented outcomes the cost of the adjuvant radiotherapy to the NHS needs to be quantified. Radical breast irradiation places substantial demands on the equipment and staff of the resources of a radiotherapy department. Indeed one report estimated that breast cancer care accounts for one third of the work of a radiotherapy department (SHPIC 1997). It has been estimated that the marginal cost per recurrence prevented by irradiation is £4415 in younger women taking into account the costs of surgery. This figure does not however take into account case mix factors such as co-morbidity. Elderly patients, for example, often place further demands on the NHS as a result of the requirement for nursing care during the course of their radiotherapy. Further economic analyses are required to establish more fully the cost-effectiveness of radiotherapy in elderly breast cancer patients.

It is the purpose of the proposed trial to determine whether adjuvant breast irradiation significantly changes the quality of life of elderly women with breast cancer treated by breast conserving surgery and adjuvant endocrine therapy, and whether this treatment is cost-effective.

3. Aims of the trial

Many women with breast cancer are able to be treated surgically by an operation which removes the cancerous lump but preserves the breast. In order to minimise the chance of the cancer recurring, they usually receive additional or 'adjuvant' treatment. In elderly women this will usually consist of taking Tamoxifen tablets for five years after the surgery, and having radiotherapy to the affected breast. The purpose of the radiotherapy is to prevent the local recurrence of disease. The use of radiotherapy carries the risk of side effects such as skin damage or rib fractures. In elderly women, these side effects can be especially troublesome. Therefore, if a subgroup of women could be identified, whose risk of cancer recurring in the breast is low, it may be questionable whether or not radiotherapy should be used.

The aim of this study is to carry out a randomised controlled trial to investigate this question in older women who have recently undergone breast conserving surgery, and are identified to have features associated with a relatively low risk of recurrence such as no tumour being present in the margins of the breast tissue which has been removed. The outcome measures on which the usefulness of radiotherapy/no radiotherapy will be assessed are: quality of life, anxiety and depression and cost-effectiveness. The cosmetic result will also be looked at as well as recurrence rates of the cancer, the short and long-term health of the patient and their functional status.

4. Plan of investigation

Women aged 65 years or more with early breast cancer at low risk of having the cancer recurring, who are attending breast cancer clinics in cancer centres will be invited to participate in the study. All patients who are over the age of 65 and have had a lumpectomy should be recorded, along with any reasons why the patient is not eligible for entry into the trial. Formal invitation to participate will be after the patient has received breast

conserving surgery to remove the cancer and once the pathology results are known, but the possibility of entering the trial may be raised earlier. Patients who are interested will be given a 'Patient Information Leaflet' and a 'Consent Form'. Those who accept will be visited at home by the research nurse, where the 'Consent Form' will be signed and collected, and the baseline questionnaire administered. Also at this visit, the patient diary for documenting the use of health and social service resources will be handed out. Patients will then be randomised to receive radiotherapy or no radiotherapy using a telephone randomisation service based in Aberdeen. All patients will receive hormonal therapy.

Data on how the patient's disease and treatment has affected their quality of life and functioning will be assessed at a further three home visits by a research sister over a fifteen month period using a standardised questionnaire. Their clinical status and morbidity will also be assessed on three occasions, at routine outpatient clinics over the year following surgery. Where facilities exist a photograph of both breasts will be taken before radiotherapy and after randomisation (and the equivalent time for non-radiotherapy patients) to assess the cosmetic effects of the treatment. This will be repeated at the twelve month post-surgery visit, along with a mammogram. Patients will be followed up longer term to monitor clinical progress in accordance with the clinics' normal procedure.

4.1 Objectives

To assess whether the omission of post-operative radiotherapy in women with low risk axillary node negative breast cancer (T0-2) treated by breast conservation with wide local excision and endocrine therapy:

- 1) improves quality of life
- 2) is more cost-effective

4.2 Design

The study is a randomised controlled clinical trial (see appendix I for plan).

4.3 Primary end-points

- 1) Quality of life
- 2) Anxiety and depression
- 3) Cost-effectiveness

4.4 Secondary end-points

- 1) Loco-regional and distant recurrence rate
- 2) Functional status
- 3) Acute and late morbidity
- 4) Cosmesis

4.5 Size of the study

We aim to recruit 120 patients per arm, a total of 240 over 3 years. With allowances for attrition due to unrelated deaths or loss to follow up, this should yield 100 evaluable patients per group. The primary outcome variables in this study are psychometric scales,

from which an assessment of the quality of life and economic costs can be made. Power calculations are presented in terms of the residual standard deviation, σ , for each variable. There is an 80% power to detect statistically significant differences at the 5% level when the difference in population means equals 0.4σ . However, the main emphasis will be on estimating benefit in several dimensions and the standard error of the mean treatment differences in any variable will be 0.15σ . Although the study is not powered to detect small differences in recurrence rates, there is 70% power to detect statistically significant differences at the 5% level if recurrence rates in the two treatment arms are 5% and 15%.

4.6 Analysis plan

The main emphasis is on quality of life, which is multidimensional, and on the economic cost of alternative treatment policies. Accordingly, we will focus the analysis on the estimation of treatment differences for all of the dimensions of quality of life, together with their standard errors, with comparable analysis of the economic variables. The principal analysis is expected to be based on a repeated measures analysis of variance, using pre-randomisation levels of each variable as a covariate for the relevant analysis. Analyses will be conducted in SAS using PROC MIXED, which overcomes many of the problems associated with the missing values, which are quite likely at later time points. Although the presentation of results will concentrate on estimation, the corresponding significance tests will be reported when this aids interpretation of the results.

In the time period of this grant, it is expected that mortality will remain too low to allow informative analysis. Loco-regional recurrences and distant metastases will be analysed using methods of survival analysis. In particular, Kaplan-Meier plots will be produced by treatment group, and the hazard ratio, and accompanying 95% confidence limits will be estimated using a Cox proportional hazards model. Variables reflecting morbidity will be summarised and analysed using standard methods for contingency tables. The measurement of cosmesis by Van Limbergen et al's (1989) method gives a distance measure. As such, it will be analysed using t-tests.

All analyses will be based on the intent-to-treat principle, and all confidence intervals and significance tests will be two-sided.

5. Eligibility criteria

- 1) Age of 65 years or more, receiving adjuvant endocrine therapy
- 2) Medically suitable to attend for all treatments and follow ups
- 3) Histologically confirmed unilateral breast cancer of TNM stages T0-2
- 4) No axillary node involvement on histological assessment
- 5) Had breast conserving surgery with complete excision on histological assessment
- 6) Able and willing to give informed consent

6. Exclusions

- 1) Past history of pure in situ carcinoma of either breast or previous or concurrent malignancy other than non-melanomatous skin cancer or carcinoma in situ of cervix
- 2) Grade III cancer with lymphatic/vascular invasion (because of higher risk of local recurrence)

7. Randomisation

Consenting patients treated by conservation surgery and adjuvant endocrine therapy will be randomised to receive or not receive breast irradiation.

Each centre will keep a register of all patients on the form provided (see appendix 2). Reasons for not entering patients in the randomised controlled trial will be recorded. Prior to surgery, patients potentially eligible to enter the trial will be identified locally. After surgery, eligibility of patients will be confirmed. Depending on local circumstances eligible patients will be invited to take part in the trial at an outpatient visit after receipt of pathology results. Patients who are interested will be given a 'Patient Information Leaflet' (see appendix 3) and will have their details forwarded to the Administrator by fax (see appendix 4). Informed written consent to participation will be obtained later by the research nurse (see appendix 5).

For those patients consenting, the randomised treatment allocation will be obtained by the clinician telephoning a randomisation service at the Health Services Research Unit in Aberdeen (see appendix 6). This service is computerised. Patient data are obtained by a mixture of recording verbal information and the clinician using the keys on any touch-tone phone. Randomisation will be balanced by centre, grade of cancer, age, lymphatic/vascular invasion, and pre-operative endocrine therapy using the method of minimisation. This method of randomisation has the advantages of being secure (not prone to entry bias), and allows some checks on patient eligibility to be made at time of randomisation. Once the patient has been formally entered into the trial by the return of the 'Randomisation Form' to the Administrator, a letter to the patient's GP will be sent (initially to the clinician for signing), informing them of their patient's participation in the trial (see appendix 7).

8. Surgical procedures

Primary surgery will consist of a wide local excision to obtain clear margins around the tumour and an ipsilateral four node lower axillary node sample or clearance. Re-excision of the margins will be carried out if required to obtain clear margins.

9. Radiotherapy planning and technique

Patients will undergo a radical course of radiotherapy to the breast alone followed by a 'boost' by electrons or iridium 192 implant to the site of the excision. The total dose, number of fractions and overall treatment time will be according to local practice in each participating centre. As a guideline 45-50 Gy over four to five weeks will be normally given at megavoltage to the breast with a boost of electrons of 10-15 Gy at an appropriate energy or an iridium 192 implant (e.g. 20 Gy to 85% reference isodose).

While participating centres will not be asked to make any significant change to current practice it will be emphasised that every precaution should be taken to minimise any significant acute or late toxicity of treatment. Specifically the following recommendations should be made:

1. All patients are simulated for radiotherapy to determine the volume of lung within the radiation treatment field. The maximum thickness of lung should not exceed 3cm;
2. The peripheral lymphatics are not irradiated;
3. A minimum of one transverse outline, taken at the central axis of the length of the tangential fields should be taken; and
4. All fields should be treated with megavoltage irradiation with wedged fields so that the dose homogeneity does not vary by more than 10%. All fields will be treated daily.

During the final week of treatment, the 'Completion of Radiotherapy Form' (see appendix 8) should be completed and sent to the Administrator to allow the timing of the first post-radiotherapy (or equivalent in the control patients) visit to be calculated.

10. Hormonal treatment

Standard therapy is Tamoxifen 20mg orally daily for five years. However, for trial purposes, all forms of adjuvant endocrine therapy will be acceptable, including pre-operative neoadjuvant therapy.

11. Follow-up arrangements

11.1 Home assessments

Quality of life questionnaires will be completed at home with the patient, by the research nurse. Initial assessment will be after surgery but prior to randomisation. Post-randomisation visits will be made within two weeks of the completion of radiotherapy (or at an equivalent time period after surgery for the control patients). Study participants will also be seen at nine months after the date of surgery to complete an approximate six month post-radiotherapy questionnaire. The longer term sequelae of the radiotherapy will be assessed at fifteen months post-surgery, using a similar questionnaire. In both instances corresponding assessments will be made in controls.

11.2 Clinic assessments

The clinic visits will be made post-operatively at around 3.5, 8 and 12 months post-surgery to fit in with standard clinical practice following radiotherapy. A 'Follow up Form' (see appendix 9) will be completed at each visit. A 'Radiation Morbidity Form' will also be completed at these times; the 'Acute Morbidity Form' (see appendix 10a) will be completed at 3.5 months only, and the 'Late Morbidity Form' (see appendix 10b) will be completed at 8 and 12 months (and at any subsequent visits within the PRIME trial) using the EORTC/RTOG scales (RTOG/EORTC SOMA scales 1995, Cox et al 1995). Although these timings may not be standard for non-radiotherapy patients, for the purpose of the trial the timing of clinic assessments will be the same. Patients will be followed up at 18, 24, 36, 48 and 60 months, or at the standard intervals within a clinic. Any recurrences are to be documented on the 'Follow up Form' and details of treatment recorded on the 'Recurrence Form' (see appendix 11), which will be sent out by the Administrator as required.

12. Data collection

The home assessment questionnaires will be returned to the Administrator on a regular basis. In order to achieve blinding of the observer when conducting home visit assessments, the research sister will ask the patient not to reveal any information relating to the treatment they have received. If this is inadvertently revealed it will be noted in the case record form.

The clinical assessment forms will be on duplicate paper, one copy of which will be sent to the Administrator after the patient's visit.

Data will be double-entered to minimise the risk of errors.

13. Quality of life assessment

Quality of life and functionality will be assessed by means of a series of standardised assessments scales covering quality of life, anxiety and depression, physical functioning and a limited number of questions covering symptoms not included elsewhere. See appendix 14 for more details.

13.1 Quality of life.

This is covered by the EORTC QLQ-C30 (Aaronson et al 1993) and QLQ-BR23 (Sprangers et al 1996) questionnaires, the Philadelphia Geriatric Center Morale Scale (Lawton 1975), and the EuroQol questionnaire (Euroqol Group 1990).

13.2 Anxiety and depression

This will be mainly covered by the HADS (Hospital Anxiety and Depression) scale (Zigmond and Snaith 1983).

13.3 Physical functioning

The Clackmannan scale (Bond and Carstairs 1982) and the Barthel Index (Mahoney and Barthel 1965) will be used to document the physical functioning.

13.4 Morbidity

During the first post-operative home visit acute symptomatology such as cough or dyspnoea as well as those covered by the EORTC QLQ-BR32 will be recorded. At the final home visit any long term sequelae will be noted on standardised proformas.

13.5 Co-morbidity

Co-morbidity information will be collected at home and at the clinic.

14. Cosmesis

14.1 Measurement systems

At centres where the facilities are available a photograph of both breasts will be taken to assess any changes in nipple position and breast contour (Van Limbergen et al 1989). These will be taken at the radiotherapy simulation appointment and its equivalent for control patients, and at twelve months post-surgery. Measurements are made of the digital image using software developed in conjunction with the Department of Medical Physics in Edinburgh (Kunkler et al 1997).

A variety of grading systems are available for the assessment of cosmesis based on a subjective comparison with the untreated breast. We propose to use the simple four point grading system devised by Harris et al (1979) which has been shown to be reliable and straightforward. This will be carried out using the photographs mentioned above.

14.2 Photography requirements

Patients should be photographed in colour, landscape format, standing with their hands on hips. The photographer must ensure that the head is excluded from the image. A 10cm scale will be taped horizontally at the level of the suprasternal notch. Normal practice for identifying patients on photographs will be observed, and, where possible, should consist of the PRIME trial identification number only. Consent for photographs to be taken need not be obtained separately, since permission has already been given by their agreement to participate in the trial. Those patients who express a desire not to have a photograph taken may still be entered into the trial, and a note made of their wishes.

Where available the first photograph will be mounted and stored locally (see appendix 12) and then forwarded with the second photograph at 12 months to the Administrator in the stiffened envelope provided. Details of the procedure will be agreed with each individual centre. Both photographs will be digitised at the Western General Hospital, Edinburgh for subsequent analysis.

15. Economic analysis

The study will address two economic questions: (1) the impact on overall resource use of local irradiation; and (2) the cost-effectiveness of local irradiation. A diary will be kept by the patient (see appendix 13) to monitor the use of health service resources (e.g. investigation and treatment of recurrent disease, visits to General Practitioners, use of social services, hospital transport). Longer term use of health service resources will be captured in the 'Late Morbidity' and 'Treatment of Recurrence' Forms. The economic analysis will be undertaken by John Cairns of the Health Economics Research Unit, University of Aberdeen.

16. Data monitoring

A Data Monitoring Committee has been established and will meet six monthly (or as often as they deem appropriate). It is composed of a statistician and two clinicians, none of whom are involved in the trial. This committee will be unblinded and will receive regular reports from the administrative centre. It will then pass on its comments and recommendations to the Steering Committee and the Executive Committee.

17. Ethical considerations

Ethical approval was sought at the Multi-centre Research Ethics Committee for Scotland on 12th March 1998 and granted on 15th October 1998.

Local ethical approval was sought and obtained before each clinic commenced the trial.

The more detailed protocol as submitted to these committees can be obtained from the study administrator.

18. Financial support

A grant has been awarded to the study by the NHS Research and Development Health Technology Assessment programme.

19. References

Aaronson, N.K., Ahmedzai, S., Bergman, B. et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;85:365-76.

Blamey, R.W. The British Association of Surgical Oncology Trial (BASO II) of the small, well-differentiated, node negative tumours. *The Breast* 1999;4:234 (abstract).

Bond, J., Carstairs, V. Services for the Elderly, Scottish Health Service Studies Number 42, Edinburgh:Scottish Home and Health Department, 1982.

Brody, J., Cassell, C.K. Normal human ageing theory, demography. In: Cassell, C.K., Riesenber, D.E., Sorensen, L. (Eds) *Geriatric Medicine: Principles and Practice*, 2nd ed. New York: Springer Verlag, 1990, pp 16-27.

Clark, R.M., Whelan, T., Levine, M. et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *Journal of National Cancer Institute* 1996;88:1659-64.

Cox, J.D., Stetz, J., Pajak, T.T. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) *International Journal of Radiation Oncology Biology and Physics* 1995;31:1341-46.

Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Part I. *Lancet*, 1992;339:1-15.

Euroqol Group. Euroqol: A new facility for the measurement of health related quality of life. *Health Policy* 1990;16:199-208.

Fisher, B., Anderson, S., Redmond, C.K. et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine* 1995;333:1456-61.

Forrest, A.P., Stewart, H.J., Everington, D. et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996;348:708-13.

Gruenberger, T., Gorlitzer, M., Soliman, T. et al. It is possible to omit postoperative irradiation in a highly selected group of elderly breast cancer patients. *Breast Cancer Research and Treatment* 1998;50:37-46.

Harris, J.R., Levene, M.B., Svensson, G., Hellman, S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *International Journal of Radiation Oncology, Biology, Physics* 1979;5:257-61.

Haynes, S.G., Feinleib, M. *Epidemiology of Ageing*. DHSS publication no. (NIH) 80-969, Bethesda, Md: DHHS, 1980.

Kunkler, I.H., Jack, W., Kerr, G.R. Computer assisted assessment of cosmesis following breast conserving therapy. Poster abstract. 9th International Brachytherapy Conference, Palm Springs, USA, 3rd-6th September 1997.

Kurtz, J.M. Factors influencing the risk of local recurrence in the breast. *European Journal of Cancer* 1992;28:660-6.

Late effects of normal tissues (LENT) consensus conference including RTOG/EORTC SOMA scales. *International Journal of Radiation Oncology, Biology, Physics* 1995;31:1065

Lawton, M.P. The Philadelphia Geriatric Center Morale Scale: A Revision. *Journal of Gerontology* 1975;30:85-89

Locker, A.P., Ellis, I.O., Morgan, D.A.L. et al. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *British Journal of Surgery* 1989;76:890-4.

Mahoney, F.I., Barthel, D.W. Functional Evaluation: the Barthel Index. *Maryland State Medical Journal* 1965;14:61-65

Nemoto, T., Patel, J.K., Rosner, D., et al. Factors affecting recurrence in lumpectomy without irradiation for breast cancer. *Cancer* 1991;67:2079-2082

Recht, A., Connolly, J.L., Schnitt, S.J., et al. The effect of young age on tumour recurrence in the treated breast after conservative surgery and radiotherapy. *International Journal of Radiation Oncology Biology and Physics* 1988;14:3-10.

Scottish Health Purchasing Information Centre. Breast Cancer Summary SHPIC publication, 1997.

Smitt, M.C., Nowels, K.W., Zdeblick, M.J. et al. The importance of the lumpectomy surgical margin status in long term results of breast conservation. *Cancer* 1995;76:259-67.

Sprangers, M.A.G., Groenvold, M., Arraras, J.I. et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire module: First results from a three-country field study. *Journal of Clinical Oncology* 1996;14:2756-68

Stroner, P. Personal Communication 1997

Thomson, C. Personal Communication 1997

Van Limbergen, E., van der Schueren, E., Van Tongelen, K. Cosmetic evaluation of breast conserving treatment for mammary cancer. I. Proposal of a quantitative scoring system. *Radiotherapy and Oncology* 1989;16:159-67.

Veronesi, U., Luini, A., Del Vecchio, M. et al. Radiotherapy after breast-preserving surgery in women with localised cancer of the breast. *New England Journal of Medicine* 1993;328:1587-91.

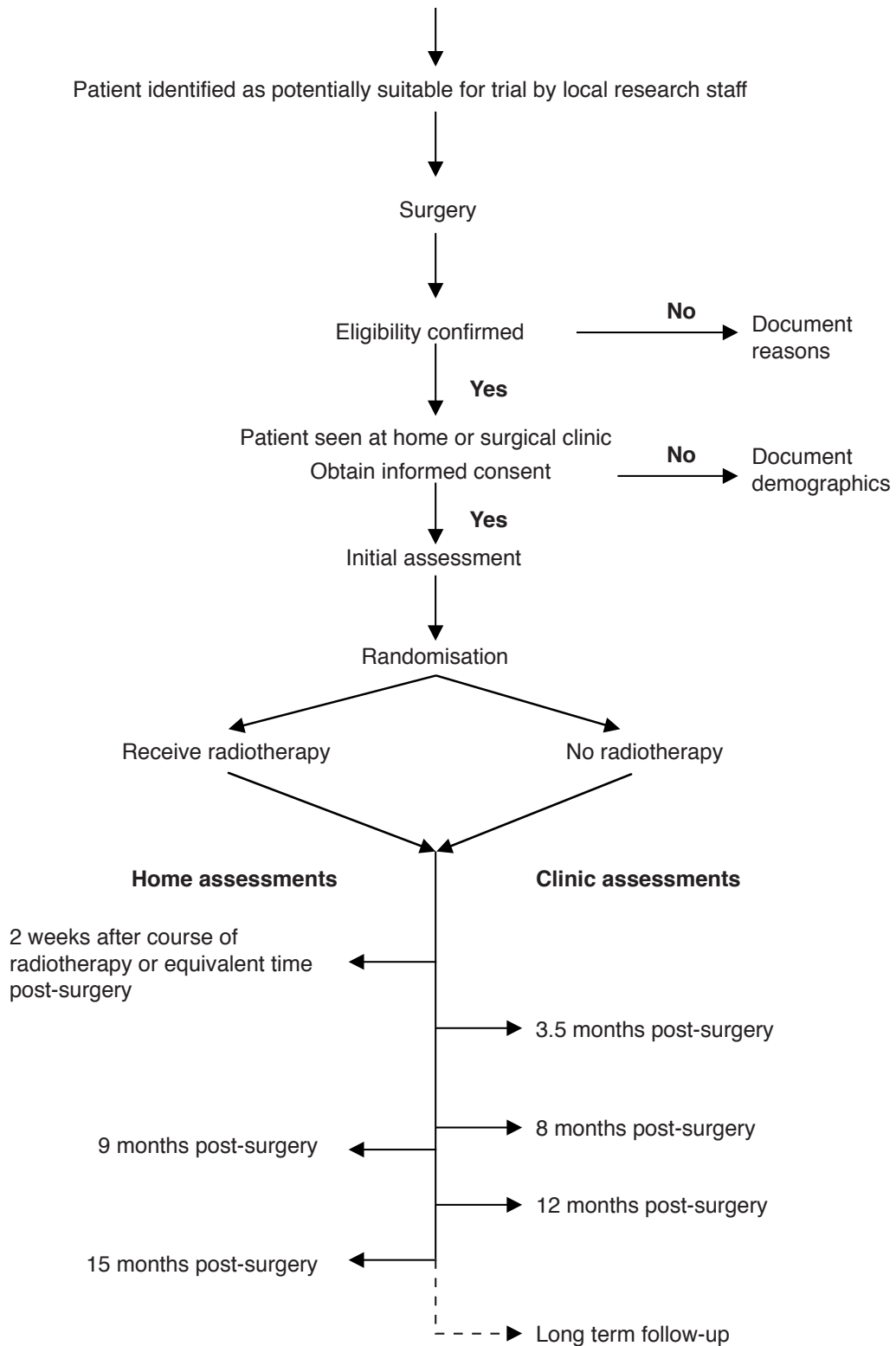
Yancik, R., Ries, L.G., Yates, J.W. Breast cancer in ageing women. A population-based study of contrasts in stage, surgery and survival. *Cancer* 1989;63:976-81.

Zigmond, A.S., Snaith, R.P. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983;67:361-70.

Appendix

- 1) Flow chart showing the progress of patients through the trial
- 2) Demographic data recording form
- 3) Patient Information Leaflet
- 4) Patient Registration Form
- 5) Informed Consent Form
- 6) Randomisation Form
- 7) Letter to General Practitioner about the trial
- 8) Completion of Radiotherapy Form
- 9) Follow-up Form
- 10) Radiation Morbidity Forms
 - a) Acute b) Late
- 11) Treatment of Recurrence Form
- 12) Photography Request Form
- 13) Example of the patient diary
- 14) Quality of Life measures

PRIME trial patient progress



Register of patients

Date begun: .

Please complete this register for every breast cancer patient who is over the age of 65 and has had a lumpectomy

[illegible]

Please send to the study administrator as each form is completed

Invitation to participate in the PRIME Study

Patient Information Sheet

We would like to invite you to take part in the PRIME (Post-operative Radiotherapy In Minimum-risk Elderly) Breast Cancer Trial. To help you decide if you would like to take part we have prepared this information sheet to give you some further details about the study which you can keep.

Introduction

You have recently been diagnosed with early breast cancer which has been completely removed by surgery. An anti-cancer drug, often Tamoxifen, will also be given as part of your treatment for five years and reduces the risk of the cancer returning. Another therapy which is currently routinely offered is radiotherapy to the breast. The radiotherapy is given to the affected breast and it is thought that it reduces the chances of the cancer coming back within the breast. There is some evidence that in older women radiotherapy may not always be needed and, like many treatments, it also has both short and long term side effects. Apart from the evidence that radiotherapy might not be needed in older women, it may not be required in women such as yourself who are at low risk of their cancer returning because your cancer: (1) has been removed with a generous margin of normal breast tissue; (2) did not have any bad features when examined by the pathologist under the microscope; and (3) has not spread to the lymph glands under your arm. On this basis we would like to ask you to take part in our study to help us decide whether radiotherapy is necessary for women with your particular type of cancer. Your specialist has indicated that he thinks that you are suitable to take part in the PRIME study.

What will I have to do if I take part?

The trial will involve 240 women who will each be followed up for 15 months. If you agree to take part you will be reviewed by a nurse either at home or in the clinic whichever is most convenient to you and you will be asked to complete a questionnaire. To determine whether or not you will receive radiotherapy, your specialist will telephone a central office which runs the PRIME study, to enter you in the study. The study office will check some details about you, your disease and the treatment you have been prescribed and will use a computer to allocate your treatment. You will have the same chance of receiving radiotherapy as you will of not receiving it. Your specialist will be told whether you have been allocated a course of radiotherapy. The nurse will arrange three visits over 15 months and on each visit you will again be asked to complete a questionnaire which will monitor how you are coping with your condition and how you are feeling and managing at home. You will also be seen three times during the first 15 months in hospital clinics for a routine examination by your specialist. This is to check that the cancer remains under control. It is also hoped to arrange a photograph of your breasts at two of your

clinic visits. This will allow us to look at changes in the breast which have occurred as a result of your treatment. At the end of the trial you will continue to be reviewed by your specialist on a regular basis. A mammogram will be done at one year after your surgery. During the trial you will be asked to keep a record of all health and social services that you received.

If you decide not to take part in the study you will receive the usual high standard treatment that is currently employed for patients with early breast cancer. You will be offered radiotherapy and be followed up at the surgical outpatient clinics in the usual way.

What does radiotherapy involve?

Radiotherapy to the breast is usually carried out over five to six weeks, usually as an outpatient. For the first attendance a series of breast measurements are taken to plan your further treatment. The radiotherapy is normally given to the breast in a small dose each day. Treatments are given for 10 to 15 minutes per day on weekdays. No treatment is given over the weekends. Four to five additional daily treatments may also be given to the site where the original cancer was excised. This extra treatment is normally given in the week following the initial course of radiotherapy to the whole breast.

What are the possible risks of taking part?

Like all treatments there may be side effects with radiotherapy. Radiotherapy may cause skin reactions leading to breast tenderness and itching. These develop in the latter part of the course of radiotherapy and usually settle within one month of the treatment finishing. Breast pain, which is usually mild and intermittent, commonly occurs up to two years post-radiotherapy, but is less troublesome thereafter. Rarely radiotherapy may cause inflammation of the lung causing shortness of breath or it may cause ribs to fracture.

The possible risk of not being given radiotherapy is that there may be a slightly higher chance of the breast cancer coming back compared to women who have received radiotherapy. However, in women aged 65 or more, we know that the chance of the breast cancer returning is lower than in younger women. Also, from our knowledge of the results of your surgery and the type of your particular tumour we believe that the risk of your cancer coming back in the treated breast is much lower than average. If your cancer did recur in your breast further surgery would be considered.

Are there any benefits from taking part?

Whether or not you take part in the study you will receive the highest standards of care. The information that we get from the study will help us gain knowledge about the best way of treating breast cancer. It will help us to measure the advantages and disadvantages of radiotherapy for women aged 65 or more who are diagnosed with early breast cancer, using assessments that are relevant to them.

Do I have to take part?

No, taking part is voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor would not be upset and your treatment would not be affected. If you take part but later change your mind you can withdraw from the study without hindrance or detriment to your future treatment. We will give you a copy of your consent form to keep.

We would want to inform your GP that you are taking part with your permission and will send him/her a copy of your consent form.

Confidentiality

All the study data will be confidential to the research team. You will not be identified in any published study results.

What do I do now?

The research sister for the trial will contact you in a day or so. She can answer any questions and you can let her know if you are interested in taking part.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Local investigator: Dr. Ian Kunkler, Consultant Clinical Oncologist, Western General Hospital, Edinburgh, EH4 2UX

If you would like to obtain independent advice about this research you may contact:

Registration Form for entry into the PRIME Trial

Post-operative Radiotherapy In Minimum-risk Elderly



Please complete for each patient who has accepted an information sheet and consent form. Consent will be confirmed by Celia King, the research nurse.

Please fax to Linda Williams on **0131 651 1631** urgently so that the patient may be contacted and visited by the research nurse as soon as possible, prior to randomisation.

Please retain this copy within the PRIME study Eligibility Record folder once confirmation of participation/non-participation has been given. A letter to the patient's GP will be sent to you for your signature if the patient has consented.

Name of Clinician: ..

Date the patient was offered participation in the trial:

Patient's name:

Patient's address:

..

Patient's date of birth:

..

Hospital number:

Patient's phone no.: .

GP's name: ..

GP's address: ...

..

GP's phone no.: ...

To be completed once the research nurse has confirmed the patient's choice

☐ Patient consented —complete the randomisation procedure. If XRT then put patient on waiting list. If no XRT then organise photograph to coincide with equivalent interval to Simulation appointment. Arrange first at equivalent to 2 weeks post-radiotherapy completion.

☐ Patient declined — arrange appropriate followup for patient's treatment choice.

☐ Wishes XRT

☐ Declines XRT

☐ Requires transport

☐ Requires accommodation



Informed Consent Form

Name of patient:

Name of clinician:

Hospital:

The aims and procedures of the clinical trial I have been asked to take part in have been explained to me by I have read and understood the patient information leaflet provided. I have been informed about the possible benefits to myself and about any reasonably foreseeable risks or discomfort, and have had sufficient time to decide.

I have had the opportunity to ask questions and consider the answers given.

I understand that participation in the trial is voluntary and that I may withdraw from the trial at any time of my own accord and that if I do, it will not affect the future care and attention which I receive from my doctors.

I understand that all records relating to this trial will be kept confidential and all data will be secure against unauthorised access.

I understand that my General Practitioner will be informed of my participation in this study and will be advised of any clinically significant information that comes to light.

I confirm that I have explained the nature of this clinical trial to the above named patient and that she has understood the explanation given to her.

Clinician's signature: Date:

I hereby freely give my consent to take part in this clinical trial.

(Signature on this form does not affect your legal rights).

Patient's signature: Date:

Witness to written consent

Name: Signature:

Relationship to patient: Date:

Further information is available from:

or

Dr. I. Kunkler, Department of Clinical Oncology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. Telephone: 0131 537 2214

POST-OPERATIVE RADIOTHERAPY IN MINIMUM-RISK ELDERLY TRIAL RANDOMISATION CHECKLIST - PAGE 1

ELIGIBILITY

All women with early non-metastatic invasive breast cancer requiring adjuvant endocrine therapy are eligible for entry into the trial provided the following criteria are met:

	YES	NO
IS THE PATIENT: (<i>Response should be YES</i>)		
aged 65 or over	<input type="checkbox"/>	<input type="checkbox"/>
medically suitable to attend for all treatments and follow-ups	<input type="checkbox"/>	<input type="checkbox"/>

HAS THE PATIENT: (*Responses should be YES*)

histologically confirmed unilateral breast cancer of TNM stages T0-T2	<input type="checkbox"/>	<input type="checkbox"/>
no axillary node involvement on histological assessment	<input type="checkbox"/>	<input type="checkbox"/>
had breast conserving surgery with complete excision on histological assessment	<input type="checkbox"/>	<input type="checkbox"/>
given consent, according to the requirements of the participating institution	<input type="checkbox"/>	<input type="checkbox"/>

HAS THE PATIENT: (*Responses should be NO*)

past history of pure in situ carcinoma of either breast or previous or concurrent malignancy other than non-melanomatous skin cancer or carcinoma <i>in situ</i> of cervix	<input type="checkbox"/>	<input type="checkbox"/>
grade III cancer with lymphatic/vascular invasion	<input type="checkbox"/>	<input type="checkbox"/>

RANDOMISATION

All patients receive breast conserving surgery and adjuvant endocrine therapy.

Patients are randomised on the basis of the information overleaf into *Radiotherapy* and *No Radiotherapy*. Please ensure that all details have been completed before phoning.

Randomisation will be performed by telephone randomisation at the Health Services Research Unit, Aberdeen.

TELEPHONE: 0800 387444

You will hear a series of pre-recorded questions to which you will be asked to respond by pressing the appropriate key on a touch-tone phone. In case of difficulty, please phone the study administrator Linda Williams on 0131 651 1631.

**POST-OPERATIVE RADIOTHERAPY IN MINIMUM-RISK ELDERLY TRIAL
RANDOMISATION CHECKLIST - PAGE 2**

Please note: There is an error correction facility within the call. By pressing '99' at the date of birth prompt and '9' at all other prompts you will be returned to the previous data entry point. This is only available up to the point of entering the response for pre-operative endocrine therapy. After that point the patient is randomised and the study number and treatment are allocated.

Patient's surname: Patient's first names:

Responsible clinician:

Patient's record number:

Referring hospital:
(of surgery)

Date of Birth: / /

Date of definitive surgery: / /

Axillary surgery: Sample ☐ Clearance ☐

Randomisation information:

Centre code:

Grade of cancer: I ☐₁ II ☐₂ III ☐₃

Lymphatic/vascular invasion: Yes ☐₁ No ☐₃

Was endocrine therapy used pre-operatively? Yes ☐₁ No ☐₃

Patient's allocated treatment:

☐ Radiotherapy ☐ No radiotherapy

Trial number: Date of randomisation: / /

Please fax this side to the study administrator on 0131 651 1631
and inform your patient of the result of the randomisation

Dear Colleague

PRIME breast cancer trial (Post-operative Radiotherapy In Minimum-risk Elderly)

I am writing to let you know that your patient Mrs/Ms of has agreed to take part in a national randomised trial to assess the need for post-operative breast irradiation in addition to adjuvant hormonal endocrine therapy, usually Tamoxifen, in women aged 65 years or more who have undergone breast conserving surgery for early breast cancer. Entry to the trial has been restricted to women who are known to have a very low risk of recurrence of the disease in whom the costs and benefits of radiotherapy, using appropriate measures such as quality of life and functional status, have not been established. Your patient is at low risk of recurrence because: there were wide clear margins on the resected breast tissue; the cancer was not aggressive histologically; and there was no evidence of axillary lymph node involvement. We wish to discover whether the removal of adjuvant irradiation, which is at present standard management, will reduce morbidity and improve the quality of life of these patients. The removal of the extra five to six weeks of hospital treatment required for radiotherapy may also reduce the NHS resources required to treat this important group of patients resulting in their more cost-effective management. In the unlikely event of a local recurrence then this may be treated by further surgery.

Your patient will be visited at home by our research sister on three further occasions over the 15 months following her surgery, at time arranged to be suitable for your patient. A structured questionnaire will be completed; the areas covered will be quality of life, anxiety and depression, functional status and morbidity secondary to radiotherapy. A diary will be completed by your patient to document health service use. Mrs/Ms will also be seen in our routine follow-up outpatient clinics three times over the year following her surgery. Assessments of morbidity, cosmesis and loco-regional and distant recurrences will be made at these routine clinics. A mammogram will be performed at one year post-surgery.

The study has been approved by the Multi-centre Research Ethics Committee and your local ethics committee. It is anticipated that 240 patients will be randomised into the trial over a three year period. A Data Monitoring Committee will meet at least six monthly to review study progress and safety. It is anticipated that the final trial report will be completed in September 2003. A copy of this will be forwarded to you on request.

For your interest I enclose a copy of the information sheet which has been given to your patient. If you have any questions about the study you may wish to contact the following local doctor who is independent of the study:

Dr.

Address

.....

Tel:

Email:

If you would like further information on the national study then please do not hesitate to contact:

Dr. Ian Kunkler, Consultant in Clinical Oncology, Department of Clinical Oncology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, Telephone: 0131 537 2214, Fax: 0131 1029

Yours sincerely,

Local Researcher

On behalf of the PRIME study team

Please complete this form during the last week of the patient's radiotherapy

Please arrange the next oncology appointment for 2 weeks post-radiotherapy

Patient's surname: .. First Names: .

Trial no.: . ..

Hospital/Clinic: .

Consultant's name: . ..

Date: .

Radiotherapy treatment

Number of days as an inpatient:

Number of days as an outpatient: .

Number of fractions: ..

Date of start of treatment: / /

Date of end of treatment: / /

Use of health service resources

Transport Number of journeys

Own	<input type="checkbox"/>	_____
Hospital Car	<input type="checkbox"/>	_____
Hospital Ambulance	<input type="checkbox"/>	_____
Other (specify)	<input type="checkbox"/>	_____

Referral to other consultants/hospitals during treatment YES / NO

If YES, specify:

Please return to the central administration in Edinburgh (address labels provided)

Please complete this form at after surgery.

Patient's surname: First Names:

Trial no.:

Hospital/Clinic:

Consultant's name:

Date of final operation (dd/mm/yy): ____/____/____

Cosmesis photograph arranged? (only at 12 months post surgery) YES / NO

Mammogram arranged? (only at 12 months post-surgery) YES / NO

Date of examination (dd/mm/yy):/...../.....

New treatment related morbidity since previous report (e.g. cough) YES / NO

Medication required YES / NO

GP visits required YES / NO

Nursing visits required YES / NO

Other (specify)

New comorbidity since previous report (e.g. stroke) YES / NO

If YES, please specify:

Alive with NO recurrence YES / NO

If YES, return form to PRIME trial office

If NO, please answer the questions below and return to the PRIME trial office. A 'Treatment of Recurrence' Form will be forwarded to you in due course.

Alive with local recurrence
(tumour in ipsilateral breast – whether considered new or recurrence) YES / NO

Alive with regional recurrence YES / NO

Alive with distant recurrence YES / NO

Diagnosis of contralateral breast primary YES / NO

If YES, please give details

Diagnosis of other cancer (not breast) YES / NO

If YES, please give details

Deceased YES / NO

Date of death (dd/mm/yy):/...../.....

Death from breast cancer ☐

Death from other causes with known recurrent breast cancer ☐

Death with NO known breast cancer present ☐

Return the top copy to the central administration in Edinburgh (labels provided)

Retain the carbonised copy in the patient's records.

Please complete this form at 2 weeks after completion of radiotherapy or at 3.5 months after surgery for non-radiotherapy patients

Patient's surname: First names:
 Trial No.:
 Hospital/Clinic:
 Consultant's name:
 Date of examination:/...../.....

Acute morbidity (EORTC/RTOG radiation morbidity criteria)

Tick one box in each category for all patients (including those not having radiotherapy)

- Skin**
- ☐ 0 : None
 - ☐ 1 : Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating.
 - ☐ 2 : Tender or bright erythema, patchy moist desquamation, moderate oedema
 - ☐ 3 : Confluent, moist desquamation other than skin folds, pitting oedema
 - ☐ 4 : Ulceration, haemorrhage, necrosis
- Lung**
- ☐ 0 : None
 - ☐ 1 : Mild symptoms of dry cough or dyspnoea on exertion
 - ☐ 2 : Persistent cough, antitussive agents, dyspnoea with minimal effort but not at rest
 - ☐ 3 : Severe cough unresponsive to narcotic antitussive agent or dyspnoea at rest, clinical or radiologic evidence of acute pneumonitis, intermittent O₂ or steroids may be required
 - ☐ 4 : Severe respiratory insufficiency; continuous oxygen or assisted ventilation

Return the top copy to the central administration in Edinburgh (labels provided)
 Retain the carbonised copy in the patient's records.

Please complete this form at after surgery

Patient's surname: First names:
 Trial No.:
 Hospital/Clinic:
 Consultant's name:
 Date of examination: / /

Late morbidity (SOMA radiation morbidity criteria)

Tick one box in each category for all patients (including those not having radiotherapy)

Breast (Objective) Grade

- oedema ☐ 0 : None
☐ 1 : Asymptomatic
☐ 2 : Symptomatic
☐ 3 : Secondary dysfunction

- telangiectasia ☐ 0 : None
☐ 1 : < 1 cm²
☐ 2 : 1 cm² - 4 cm²
☐ 3 : > 4 cm²

- fibrosis ☐ 0 : None
☐ 1 : Barely palpable increased density
☐ 2 : Definite increased density and firmness
☐ 3 : Very marked density, retraction and fixation

- retraction/atrophy ☐ 0 : None
☐ 1 : 10% - 25%
☐ 2 : > 25% - 40%
☐ 3 : > 40% - 75%
☐ 4 : Whole breast

- ulcer ☐ 0 : None
☐ 1 : Epidermal only, ≤ 1 cm²
☐ 2 : Dermal, > 1 cm²
☐ 3 : Subcutaneous
☐ 4 : Bone exposed, necrosis

Breast (Management)

- pain ☐ 0 : None
☐ 1 : Occasional non-narcotic
☐ 2 : Regular non-narcotic
☐ 3 : Regular narcotic
☐ 4 : Surgical intervention

Grade

- oedema ☐ 3 : Medical intervention
☐ 4 : Surgical intervention/
 mastectomy

- ulcer ☐ 2 : Medical intervention
☐ 3 : Surgical intervention/wound debridement
☐ 4 : Surgical intervention/mastectomy

- atrophy ☐ 4 : Surgical intervention/
 mastectomy

RTOG/EORTC criteria

- Lung** ☐ 0 : None
☐ 1 : Asymptomatic or mild symptoms (dry cough). Slight radiographic appearance
☐ 2 : Moderate symptomatic fibrosis or pneumonitis (severe cough). Low grade fever; patchy radiographic appearances
☐ 3 : Severe symptomatic fibrosis or pneumonitis. Dense radiographic changes
☐ 4 : Severe respiratory insufficiency/continuous O₂/assisted ventilation

- Bone** ☐ 0 : None
☐ 1 : Asymptomatic, reduced bone density
☐ 2 : Moderate pain or tenderness, irregular bone sclerosis
☐ 3 : Severe pain or tenderness, dense bone sclerosis
☐ 4 : Necrosis, spontaneous fracture

Return the top copy to the central administration in Edinburgh (labels provided)

Retain the carbonised copy in the patient's records

Please complete this form should the patient have any evidence of local/distant recurrence since the last examination

Patient's surname: .. First Names: . . .

Trial no.: . . .

Hospital/Clinic: . . .

Consultant's name: . . .

Date of examination (dd/mm/yy): / /

Cytological/histological confirmation

Details of recurrence	Confirmation?	DATE dd/mm/yy
Local recurrence (LR)	YES / NO	/ /
Regional recurrence (RR)	YES / NO	/ /
Contralateral breast primary	YES / NO	/ /

Further Investigation (please tick)

Mammogram	<input type="checkbox"/>	Liver Function Test	<input type="checkbox"/>
Fine Needle Aspiration	<input type="checkbox"/>	Chest X-ray	<input type="checkbox"/>
Core Biopsy	<input type="checkbox"/>	Bone Scan	<input type="checkbox"/>
Breast Ultrasound	<input type="checkbox"/>	Liver Ultrasound	<input type="checkbox"/>
Full Blood Count	<input type="checkbox"/>	MRI scan	<input type="checkbox"/>
		CT scan	<input type="checkbox"/>

Further Treatment required (please tick)

Breast surgery — Wide Local Excision ☐ Date of surgery: / /
 — Mastectomy ☐ Date of surgery: / /

Axillary surgery — Sample ☐
 — Clearance ☐

Systemic Therapy - Endocrine
 - Cytotoxic

Specify:

.....

Radiotherapy - Breast ☐
 - Breast and axilla ☐

If Radiotherapy is required:
 Number of fractions: _____
 Number of days as outpatient: _____
 Number of days as inpatient: _____

Transport
 Own ☐ Number of journeys _____
 Hospital Car ☐ _____
 Hospital Ambulance ☐ _____
 Other (specify) ☐ _____

Palliative care ☐

Please return to the central administration in Edinburgh (address labels provided)



Clinical Photography request
PRIME Breast Cancer Trial
Post-operative Radiotherapy In Minimum-risk Elderly

<p>Patient's name:</p> <p>Hospital no.:</p> <p>PRIME no.:</p> <p>Consultant/Registrar:</p> <p>Date:</p> <p style="text-align: right; font-size: small;">Please use label if preferred</p>	
<p>Requirements:</p> <p><u>View</u> — Frontal of both breasts standing with hands on hips</p> <p><u>Scale</u> — 10cm length strip at supra-sternal notch</p> <p><u>ID</u> — PRIME trial number to be written on the back of each image</p> <p><u>Print</u> — 5 x 4 colour landscape</p> <p><u>Storage</u> — Mount first print on below left. Retain until 2nd print mounted and return prints to study administrator in the envelope provided.</p>	
<p>Camera —</p> <p>Lens —</p> <p>Lighting —</p>	<p>Tripod height —</p> <p>Distances —</p>
<p>Date of first photograph:</p>	<p>Date of second photograph:</p>

Please complete this section in addition to the table inside.

Date	Medication	Dose

PLEASE FOLD HERE

Hospital:

Study Nurse:

Study Co-ordinator:

..

Celia King

Linda Williams

☎ 0131 664 5977 (tel/fax)

☎ 0131 651 1631 (tel/fax)

☎ 0790 155 5727 (mobile)

PRIME

Post-operative Radiotherapy In Minimum-risk Elderly Breast Cancer Trial

Diary number:

Patient Name:

Patient Trial No:

PATIENTS —Please ask any medical or nursing personnel whom you see for any reason during this study to complete the details overleaf. If you forget, please fill in as best you can. THERE IS NO NEED TO RECORD VISITS TO THE RADIOTHERAPY DEPARTMENT (IF APPLICABLE) AS THIS WILL BE RECORDED AT THE END OF RADIOTHERAPY.

Doctors, Nurses etc. —Please complete this Diary at every contact with this study patient (excluding radiotherapy treatments). It will only take a few seconds but is vitally important for this study. Thank you for your co-operation

Quality of Life Measures

EORTC QLQ-C30 and QLQ-BR23

The scale of the European Organisation for Research and Treatment of Cancer (EORTC) study group on Quality of Life was developed for use as a brief standardised quality of life measure which could be used in international cancer trials. The model of quality of life used for this scale is multidimensional and covers cancer-specific symptoms of disease, the side-effects of treatment, psychological distress, physical functioning, social interaction, global health and quality of life. The 30-item version (QLQ-C30) may be self-administered and takes around 10 minutes to complete (Aaronson et al 1993). Most of the questions have a hierarchical response (Not at all; A little; Quite a bit; and Very much), with two questions relying on the use of a visual analogue scale. The questions are summed to produce sub-scales. The QLQ-C30 has undergone extensive psychometric testing which has yielded favourable results. In light of these considerations the proposed research will employ the QLQ-C30 as a general cancer quality of life scale. In addition it will also use the QLQ-BR23 (Sprangers et al 1996) which is the breast cancer module which has been designed to supplement the QLQ-C30. This 23 item scale includes cancer specific symptoms as well as problems of the breast, armpit, arm, shoulder and skin. It has also undergone psychometric testing. Three of the questions relate to sexual functioning and enjoyment, and may be omitted if the patient declines to answer.

Philadelphia Geriatric Center Morale Scale

This scale was developed specifically for use in the elderly (Lawton 1975) and has been found to be highly acceptable to them. A joint working party from the Royal College of Physicians and the British Geriatrics Society (Royal College 1992) recommended it as one of a series of research instruments for the assessment of the morale of older persons. It is comprised of 17 questions which have a yes/no format taking between 5 and 10 minutes to complete. All questions within the scale are given equal weight yielding a maximum possible score of 17 indicating a very high morale. The overall scale may be sub-divided into 3 sub-scales; Agitation, Attitude Toward Own Ageing, and Lonely Dissatisfaction. There are no reference standards for this scale. Psychometric testing has been favourable.

EuroQoL

This is a generic scale used to assess health-related quality of life (Euroqol Group 1990). It is comprised of two parts and only takes a few minutes to complete. The first section has five questions covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with three response levels. The questionnaire classifies patients into one of 243 health states. The second part asks the patient to indicate their own perceived health on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state). The scale has undergone considerable psychometric evaluation.

Anxiety and Depression

Hospital Anxiety and Depression Scale

It is recognised that many of the scales designed to investigate psychiatric conditions and psychological morbidity contain questions relating to physical illness. For this reason,

together with its simplicity, the Hospital Anxiety and Depression scale is being included in the present study (Zigmond and Snaith 1986). This scale, which is widely used in oncology, comprises 14 items with 4-point response scales. The individual items are scored from 0-3 to 3-0 depending upon the direction of the item wording. Higher scores are indicative of problems. Cut-off points have been established for the depression sub-scale. The reliability and validity of the scale have been tested by its developers.

Physical functioning

The Barthel Index

The Barthel Index (Mahoney and Barthel 1965) is extensively used to assess the primary activities of daily living. It is one of the recommended scales of the joint working party from the Royal College of Physicians and the British Geriatrics Society for the assessment of older people. It is comprised of 10 questions, seven of which address self-care and the remainder mobility. The scores for the individual questions are summed and may range from 0 to 20, with higher scores indicating more independence. It is recognised that the scoring system is rudimentary and changes in a given number of points do not reflect equivalent changes in disability across different activities. The Index is not useful for small impairments and is limited by ceiling effects. Reference standards have been suggested by the joint working party to indicate differing degrees of dependency. The Index has undergone extensive psychometric testing.

Clackmannan Scale

To help overcome the ceiling effect identified by the joint working party in relation to the Barthel Index the Clackmannan Scale (Bond and Carstairs 1982) was included in the current study. This scale assesses the instrumental activities of daily living, as well as the primary activities (self-care and mobility), giving three sub-scales. The sub-scales may be added together to give an overall score. Scores may range from 0 to 30 with lower scores being indicative of a higher level of functioning. It will have more sensitivity to detect any functional differences between the two groups of our study population than the Barthel Index. The Clackmannan Scale was specifically constructed for the purpose of surveying elderly people in the community and in institutional care. The elderly find the scale acceptable and it has been widely used for community surveys in Britain. Considerable developmental work went into designing the scale and a limited amount of psychometric testing has been performed.

References

Aaronson, N.K., Ahmedzai, S., Bergman, B. et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;85;365-76.

Bond, J., Carstairs, V. *Services for the Elderly*, Scottish Health Service Studies Number 42, Edinburgh:Scottish Home and Health Department, 1982.

Euroqol Group. Euroqol: A new facility for the measurement of health related quality of life. *Health Policy* 1990;16:199-208.

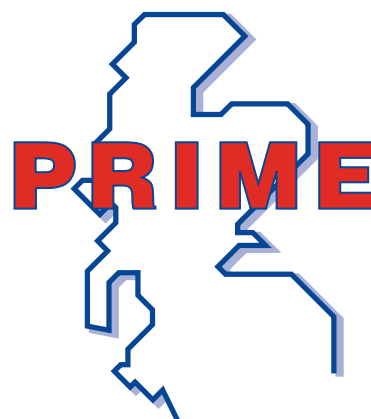
Lawton, M.P. The Philadelphia Geriatric Center Morale Scale: A Revision. *Journal of Gerontology* 1975;30:85-89

Mahoney, F.I., Barthel, D.W. Functional Evaluation: the Barthel Index. *Maryland State Medical Journal* 1965;14:61-65

Royal College of Physicians of London, and the British Geriatric Society, *Standardised Assessment Scales for Elderly People. A report of joint workshops of the Research Unit of the Royal College of Physicians and the British Geriatric Society*, London: Royal College of Physicians of London, 1992.

Sprangers, M.A.G., Groenvold, M., Arraras, J.I. et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire module: First results from a three-country field study. *Journal of Clinical Oncology* 1996;14:2756-68

Zigmond, A.S., Snaith, R.P. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983;67;361-70.



Trial Personnel

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