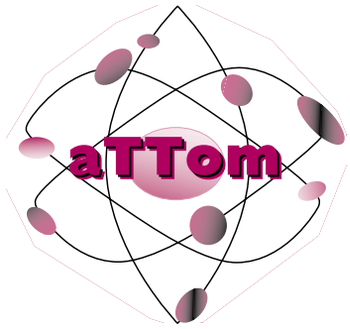


PROTOCOL

A large, uniquely simple, randomised study to assess much more reliably the balance of benefits and risks of prolonging adjuvant tamoxifen treatment in early breast cancer.

Trials of adjuvant tamoxifen in women with early breast cancer have demonstrated a highly significant improvement in 15 year survival. However, it is, as yet, not known how long women with early breast cancer should continue to take tamoxifen. Most trials of tamoxifen versus no tamoxifen involved only 1, 2 or 5 years of treatment, with trials that studied the longer tamoxifen durations showing the greatest benefit. Direct randomised comparisons of 2 years of tamoxifen with 5 years have now confirmed that, within this range, longer treatment reduces the risk of recurrence – although no clear survival advantage is yet apparent. These results suggest that 2 years treatment may not be long enough, but there is very little randomised evidence to know whether or not there is any added therapeutic advantage for longer than a few years treatment. Moreover, while tamoxifen has relatively few short term or medium term side effects (particularly for post-menopausal women), there is an increasing risk of developing endometrial cancer with longer treatment and, in addition, tamoxifen could have some other long-term side effects which may also increase if the drug is taken for many years. Hence, although there are reasons to be optimistic that longer term tamoxifen will be even more effective, the balance of benefits and risks needs to be determined much more reliably.

Even if longer term tamoxifen prevented just 2 or 3 deaths per hundred women treated, in such a common disease this would translate into tens of thousands of lives saved world-wide each year. Or, if longer term treatment produced no worthwhile extra survival benefit, then reliable demonstration of this could avoid the unnecessary prolonged treatment of many hundreds of thousands of women. What is needed is much larger scale, randomised evidence to provide a clear answer.

aTTom aims to randomise many thousands of women between stopping tamoxifen after some years of treatment versus continuing treatment for at least five extra years. Eligibility criteria are pragmatic with randomisation taking place at the point when **substantial uncertainty** arises as to whether to stop or to continue tamoxifen. To make large scale recruitment possible from even the busiest clinics, the **aTTom protocol is kept very simple with minimal workload required from participating clinicians.**

aTTom is organised by the United Kingdom Co-ordinating Committee on Cancer Research and is funded by the Cancer Research Campaign, The Imperial Cancer Research Fund and the Medical Research Council

"One may speculate whether the benefit from tamoxifen could be even greater if treatment were extended beyond 5 years.....A statistically reliable conclusion will probably require a randomised comparison involving several thousand patients"

Swedish Breast Cancer Cooperative Group, Journal of the National Cancer Institute Vol. 88, 1543-1549, 1996

"Clearly, the analysis of results from other current or planned studies must be undertaken to settle the issue of the optimal duration of treatment of tamoxifen"

Eastern Cooperative Oncology Group, Journal of the National Cancer Institute Vol. 88, 1828-1832, 1996

"It is essential to provide reliable data for future generations of women with breast cancer. For such a common disease, determining the optimum duration of tamoxifen therapy is vital"

Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group, Journal of the National Cancer Institute Vol. 88, 1834-1839, 1996

"More precise estimates of the benefit and risk from long-term tamoxifen would be welcome, and we would urge participation in ongoing trials addressing this question"

Scottish Cancer Trials Breast Group, British Journal of Cancer, 74, 297-299, 1996

"Two large international studies that are in progress are aTTom and ATLAS.....These trials should answer more definitely the question of the optimal duration of tamoxifen therapy"

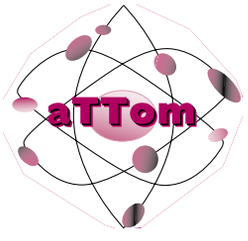
Sandra M. Swain, Medical Director, Comprehensive Breast Center, Washington DC, Journal of the National Cancer Institute Vol. 88, 1510-1512 (Editorial) 1996

"Every year almost one million women develop breast cancer, and premature certainties as to whether adjuvant tamoxifen therapy should be stopped after 5 years could lead to many unnecessary deaths"

Richard Peto, Journal of the National Cancer Institute Vol. 88, 1791-1793 (Editorial) 1996

"I believe that you will be completing one of the most important studies this century"

Professor V Craig Jordan, on the aTTom study, December 1996



aTTom Study Office

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NOTES

BACKGROUND

Tamoxifen: an effective treatment for breast cancer

Breast cancer is the most common cancer among women in developed countries. World-wide there are 800,000 new breast cancers diagnosed each year with 30,000 in the UK alone, and an annual mortality of approximately 15,000. Encouragingly, the death rate is now falling in the UK and elsewhere, which is at least partly attributable to the widespread use of tamoxifen after surgery[1-4]. World-wide, more than a million women are now using the drug in the adjuvant setting, resulting in the prevention of tens of thousands of deaths each year. The world-wide overview reviewed data on 36,000 women in 55 trials of tamoxifen who were randomised between no tamoxifen and a duration of 1, 2 or 5 years treatment[1-4]. The results show a moderate but highly significant improvement in 15 year survival in the treatment group (overall about 6% absolute difference), with the greatest improvement seen in trials that used longer tamoxifen treatment durations.

Trials of 2 vs 5 years treatment

There now exists convincing evidence from directly randomised comparisons of 2 vs 5 years that longer treatment provides an advantage for women in terms of disease-free and, probably, overall survival. The publication of two trials in particular will do much to persuade clinicians that 2 years adjuvant tamoxifen is inferior to longer treatment, at least for women with ER positive tumours.

The Swedish Breast Cancer Co-operative Group randomised 3,455 women between either stopping treatment after two years or continuing to five years[5]. Survival at 10 years was 80% among the patients in the five year group compared to 74% in the two year group (p=0.03). The CRC 'over- 50' study, also comparing five versus two years of tamoxifen, included 2,937 women and reported significantly fewer relapses and a trend towards better survival with five years treatment[6].

Trials of 5 years vs longer treatment

At present, little direct randomised evidence exists as to whether longer than a few years treatment provides any additional survival benefit[7-9]. The publication of findings from two American studies comparing 5 years with 10 years of tamoxifen treatment has, if anything, added to the prevailing uncertainty as to which treatment duration is optimal. Results from the NSABP B-14 study[8] - on which the clinical announcement by the National Cancer Institute recommending 5 years treatment in routine practice was based - favour five years treatment rather than 10, but a parallel study by the ECOG group[9] suggests the opposite. These statistically incompatible findings are probably explained by the small numbers of recurrences seen in both of these studies. The unexpected findings from the NSABP study may also be partly explained by the study having closed early on the recommendation of its Data Monitoring Committee. Unfortunately, this committee was not aware at the time of the apparently favourable ECOG results which seriously undermine the hypothesis that long-term tamoxifen may actually be harmful by stimulating instead of inhibiting tumour growth. So, although the first generation of tamoxifen duration trials have narrowed the range of uncertainty about the optimal treatment duration, they have failed to answer the key question of when, if at all, the balance of benefits and risks no longer favours continued treatment.

Tamoxifen - increasing benefits and increasing risks with longer treatment

As well as its effects in prolonging disease-free and overall survival, an additional benefit from tamoxifen is to reduce the number of contralateral breast cancers by almost a half in studies of longer term tamoxifen treatment[4]. Tamoxifen also has beneficial pro-oestrogenic activity in terms of a reduction in post-menopausal bone loss and a reduction in serum low density lipoproteins[10,11]. While in the short term tamoxifen has few serious side effects there is concern over the longer term effects, particularly the increased risk of developing endometrial cancer[12-15]. During the first few years of tamoxifen therapy the increase in endometrial cancer is heavily outweighed by the decrease in breast cancer recurrence. However, the risk of developing tamoxifen-induced endometrial cancer increases with longer treatment, and it is possible that, if the drug is taken for many years, then this could alter the balance of benefits and risks against tamoxifen.

The aTTom Study: a much more reliable assessment of the balance of benefits and risks

There are reasons to be optimistic that further survival benefits can be achieved by prolonging tamoxifen treatment for even longer than a few years. This is, literally, a question of vital importance for more than a million women around the world who are currently taking the drug. But, so far trials comparing longer than 2 years tamoxifen have recorded only a few dozen recurrences and so cannot answer this pressing question. What is needed is much larger-scale randomised evidence for a clear answer to emerge.

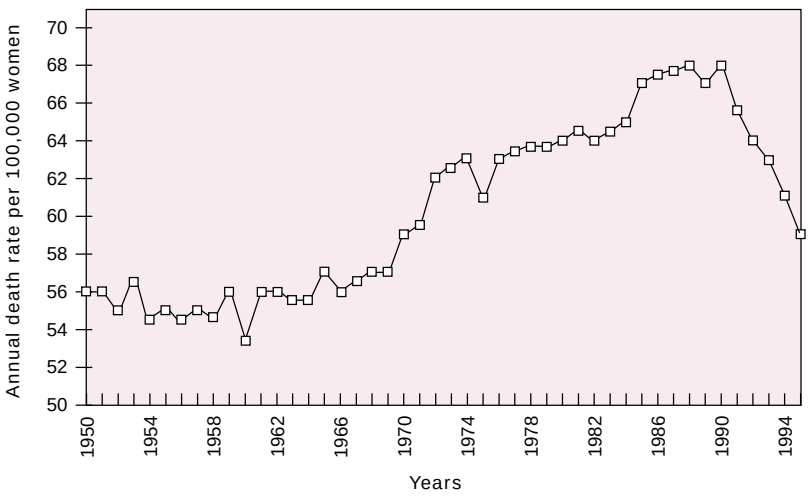
aTTom is a large, uniquely simple, randomised trial set up to provide this answer.

THE aTTom STUDY

Why is aTTom so important?

In terms of deaths avoided, tamoxifen is probably the most effective form of medical oncology currently used and world-wide, with more than a million women now using the drug in the adjuvant setting, tamoxifen is saving tens of thousands of lives each year. As a result, the patterns of breast cancer mortality are now changing so that in the UK and elsewhere, there is a sharp downward trend in mortality which is at least partly attributable to adjuvant tamoxifen[16]. Whether further benefits are achievable by longer tamoxifen is obviously an important question since the answer is directly relevant to the treatment of several hundreds of thousands of women.

Breast Cancer Mortality 1950-1994, UK
(mean of rates at ages 20-79)



Why do we need such a big study?

However, the simple question of how long to continue tamoxifen treatment is surprisingly hard to answer for two main reasons. First, studies of this question would have to be much larger than has been generally recognised. Small-scale studies carry the substantial risk of getting the wrong answer because the results are unduly influenced by favourable or unfavourable random fluctuations, particularly if frequent interim analyses are carried out before sufficient numbers of events have been allowed to occur. Second, tamoxifen has a substantial 'carry over' benefit with fewer recurrences seen for a few years after the end of the treatment period. This means that in trials comparing shorter versus longer regimens, for the first few years of additional treatment, there may be little or no extra benefit apparent but, later on, worthwhile benefit may emerge. In other words, the carry-over effect means that the balance of risks and benefit may change during the follow-up period. Therefore, trials of two versus five years of tamoxifen may need 10 years rather than five years of follow-up and trials of five versus 10 years may need 15 years rather than 10 years of follow-up before a clear picture emerges of the overall balance of benefits and risks. The early stoppage of the NSABP B-14 trial and the subsequent NCI clinical alert may well be shown, in the course of time, to have been inappropriate since, with longer follow-up, the balance of benefits and risks may change.

Large, pragmatic trial design

aTTom will compare the disease-free and overall survival of women who are randomised to stop adjuvant tamoxifen with those randomised to continue for at least 5 extra years. Randomisation takes place at the point when the responsible clinician becomes **substantially uncertain** as whether to stop or to continue tamoxifen treatment.

Entry into the study is by a single phone call (or fax) to the study office when basic patient details are collected and a treatment allocation given. Thereafter, only the minimal amount of follow-up data needed to compare outcomes is collected at yearly intervals.

Wide entry criteria

Any woman who has had a histologically proven breast cancer completely excised, who is clinically relapse free, and who is currently taking tamoxifen can join the aTTom study. The patient is eligible if there are not thought to be any clear indications for, or definite contra-indications against further tamoxifen, and hence substantial uncertainty exists as to whether to stop or to continue treatment.

Definite contra-indications to tamoxifen are specified not by the protocol, but by the judgement of the responsible physician and might include:

- Intended or actual pregnancy or breast feeding
- Significant endometrial hyperplasia
- retinopathy
- need for anti-coagulant therapy (a contra-indication to tamoxifen)
- serious toxicity (e.g: depression) thought to be due to tamoxifen

Or

Conditions associated with only a small likelihood of worthwhile benefit, e.g.

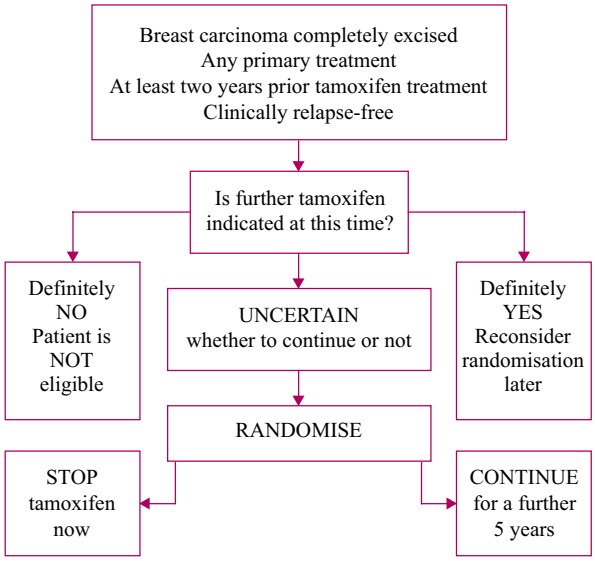
- Negligibly low risk of breast cancer death
- some major life threatening disease other than breast cancer (such that management of breast cancer risk is not the main concern)
- low probability of treatment compliance (e.g.psychiatric disorder, extreme old age)

Women who have received any type of initial surgery and who have received any other type of adjuvant treatment are eligible for aTTom. Women may have node-positive or node-negative disease, be pre- or post-menopausal, and have ER-positive or ER-negative tumours, etc. These wide entry criteria should ensure large scale recruitment of an appropriately heterogeneous population. Heterogeneity of the types of patients randomised increases the medical value of the study as it will provide valuable information as to which patients benefit most and whether previous treatments influence the efficacy of tamoxifen.

When uncertainty arises - randomise

There is considerable variability in the length of time that women with breast cancer are prescribed adjuvant tamoxifen. Some doctors prescribe tamoxifen for just 2 years, some for around 5 years and others for life. Individual clinicians have different practices for different patients that depend on the patient's age, risk factors, presence or absence of detectable hormone receptors on the primary tumour, and how well tamoxifen is tolerated. Moreover, as new evidence emerges, clinical practice changes. This heterogeneity of clinical opinion means that different doctors might recommend different durations of treatment to be suitable for the same individual. The aTTom study therefore adopts a pragmatic approach: randomisation takes place at the point when the woman and her doctor become **substantially uncertain** as to whether to stop or to continue tamoxifen.

aTTom trial design



Any woman who has received at least 2 years tamoxifen treatment can be randomised at any point thereafter.

Compatibility with other clinical trials

aTTom is addressing one of the many important issues in breast cancer today. Other trials that do not include a randomisation for tamoxifen duration are compatible with aTTom. Hence women may already have been entered into studies addressing other aspects of breast cancer treatment before they join the aTTom study.

In particular, as aTTom is relevant to women who have been diagnosed some years previously, it does not compete for patients with most other ongoing trials that are investigating earlier treatment.

The Atlas trial

Atlas, co-ordinated from the Clinical Trial Service Unit in Oxford, is the international counterpart to aTTom and like aTTom aims to randomise about 20,000 women between stopping tamoxifen treatment or continuing for an extra 5 years. Atlas and aTTom are complementary, following a common protocol and the two research teams running the trial work closely together.

aTTom TRIAL PROCEDURES

Randomisation

Each time the future treatment of a patient who is already receiving adjuvant tamoxifen is reviewed, consider whether continuing treatment is clearly indicated. If you and your patient are substantially uncertain as to whether or not to continue tamoxifen treatment, then she can be offered the opportunity to take part in the aTTom study.

At randomisation you will be asked to provide patient identification details as well as details of any previous treatments. Before randomisation it may help to complete the pre-randomisation checklist which covers all of the information you will be asked for when you call the aTTom study office 0800 371 969 or 0800 731 7625. Alternatively randomisations can be faxed to the study office (0800 731 7625). Once we have recorded the patient details an immediate treatment allocation will be made either to stop tamoxifen treatment or to continue for at least 5 extra years. Written confirmation of the patient details and the treatment allocation will be sent to you shortly after randomisation.

Pre-Registration option

To make it easier for you to take part in aTTom, patients who are prescribed tamoxifen may be registered following their initial surgery or at any time thereafter. You will be asked to provide the same patient details at registration as you would at randomisation and to stipulate when you intend to review the need for further tamoxifen. Towards the end of this initial period on tamoxifen we will remind you that this patient is due for randomisation.

Please see appendix I for a copy of the registration and randomisation form.

Minimal data collection - *no extra investigations or follow-up visits*

aTTom is designed as a large simple trial involving virtually no extra work for the clinician. To make it practicable for even the busiest clinicians to take part, the need to collect extensive information on each patient has been avoided. Investigations and management of patients differ at different centres and it is not appropriate to impose rigid patient management procedures or extra investigations. aTTom therefore adopts a pragmatic approach with clinical responsibility for all aspects of the management of the patient remaining with the patients' own doctor.

For data monitoring purposes we do need to collect some data on recurrences and on any serious side effects of treatment. The current status of all patients will therefore be ascertained through annual follow-up which will consist of a simple form requesting just one line of data per patient. For patients who no longer attend regular hospital clinics (or upon request), follow-up information will be obtained through patients' GPs. Long-term follow-up of mortality and second cancers will be obtained through the Office of National Statistics and Cancer Registry.

Please see appendix IV for a copy of the annual follow-up form.

Serious adverse events

Tamoxifen is usually well tolerated and only rarely causes side effects severe enough to require stopping treatment. However, not enough experience of very long-term use of tamoxifen exists. Any serious and unexpected adverse events, believed to be caused by tamoxifen, should be reported to the aTTom study office, without delay.

Serious adverse events are those that are fatal, life-threatening, disabling and/or incapacitating, require hospitalisation or which is a congenital anomaly, a new cancer or is an overdose. **Unexpected** events are those which do not appear in the current tamoxifen data sheet. If a patient becomes pregnant, tamoxifen therapy must be stopped immediately. In addition, as part of normal practice, clinicians are expected to follow their usual procedures for adverse event reporting. Information on serious and unexpected adverse events will be reported to the Data Monitoring Committee.

To report serious unexpected adverse events

☎

0121 414 3796

ANALYSIS

The objective of the trial is to detect reliably, or refute reliably, any overall survival benefit from extending the duration of therapy with adjuvant tamoxifen.

Information on date and cause of death, and on second cancers, for each patient randomised, will be obtained from the responsible clinician and/or National Records. All analyses will use the logrank method and include all randomised patients on an 'intention to treat' basis. All-cause mortality will be the principal endpoint. This analysis will be complemented by subsidiary analyses of recurrences and of deaths believed to be due to breast cancer. Deaths from other primary tumours - in particular, endometrial and liver cancer - will also be examined as will deaths from cardiovascular causes. The analyses will be stratified by the duration of tamoxifen given prior to randomisation (2-3yr, 4-5yr, 6-7yr, 8-9yr and 10+yrs), by age (<49, >50), and by important prognostic factors, including tumour type and grade, nodal and ER status. Pre-specified subgroup hypotheses are that any reduction in recurrence and death will be larger for women with ER-positive tumours than ER-negative (who may derive no worthwhile benefit), and that a survival benefit from longer term tamoxifen will not emerge until at least 2 years after randomisation.

Number of patients needed

In order to confirm,or refute, a 3% difference in absolute survival (e.g.75% to 78%), 8,000 patients would have to be randomised to have a 90% chance of detecting this difference (at a 5% statistical significance level) between the two groups. To detect a 2% difference in absolute survival (e.g.75% to 77%), 20,000 patients would be needed. aTTom therefore aims to randomise a minimum of 8,000 women and will continue to 20,000 if feasible and if a clear answer has not emerged earlier. It is likely, though, that 20,000 will only be achievable through a meta-analysis of aTTom with Atlas and other similar studies.

This number is considerably larger than in any previous cancer trial, but it is not disproportionately large if, during the years after the trial ends, the results will be of direct relevance, to many hundreds of thousands of women world-wide for whom long-term tamoxifen treatment is being considered.

How long will the trial continue?

If, as we all hope, the survival benefit from longer tamoxifen is substantially greater than 2%, then this would become apparent well before 20,000 patients are randomised. In the patients best interests, an independent data monitoring committee (DMC) will review up-to-date analyses of mortality (and other major endpoints) at yearly intervals - or more frequently if thought appropriate. If the benefits or harm of longer term tamoxifen are established beyond reasonable doubt - for all or some classes of women - then the steering committee will be notified and trial entry will be amended accordingly. The DMC will use the best ethical, scientific and statistical principles to guide their decision.

Compliance

A survey of the first 500 patients randomised has been conducted through GP questionnaire and indicates a high level of treatment compliance. Compliance will continue to be monitored throughout the study from annual follow-up data.

Ethical Approval

The study must have the approval of the relevant Local Ethics Committee before patients are entered. Written informed consent should be obtained from the patient before randomisation. An example of a patient information sheet is given in appendix III and, where appropriate, the aTTom co-ordinators will be happy to adapt this to meet participants individual requirements or those of the Local Research and Ethics Committee.

The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the trial, the responsible clinician is free to give any other treatment or to change the duration of tamoxifen where this is considered to be in the patient's best interests. Similarly, the patient is free to withdraw from the study without giving any reason and without prejudicing further treatment.

Financial Support

aTTom is organised by the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) breast cancer sub-committee. It is jointly funded by the Cancer Research Campaign, the Imperial Cancer Research Fund and the Medical Research Council.

Indemnity

The aTTom trial is being run by the UKCCCR independently of any pharmaceutical company. As such, it is not covered by the ABPI guidelines on non-negligent liability. The UKCCCR does not hold insurance against claims for compensation for injury caused by participation in clinical trials and they cannot offer any indemnity. However, it should be stressed that in terms of liability, NHS Trust and non-Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial.

Publication

The success of the study depends entirely on the commitment and efforts of all of those taking part. Credit for the results will be given to all of those who have collaborated in the study (not just the trial organisers), especially the women who have taken part.

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APPENDIX I

Registration and Randomisation form

The following information is required to register and/or randomise a patient into the aTTom study. For immediate registration and randomisation please call the study office 0800 371 969 or 0800 731 7625 to provide us with these details. Or, alternatively, the form may be faxed on 0800 731 7625 or returned in the free post envelope provided.

Adjuvant Tamoxifen Treatment - Offer More?

REGISTRATION AND RANDOMISATION

For IMMEDIATE Registration and Randomisation, call 0800 371 969 or 0800 731 7625 or fax this form to 0800 731 7625

Responsible Consultant: ..... **Hospital:** .....

Today's Date: ..... **Name of Person calling:** .....

Patient Details: Please fill in all available details, or attach a hospital label

Forename(s): ..... **Surname:** .....

Address: .....

Date of Birth: ☐☐/☐☐/☐☐☐☐ (Day/Month/Year) **Sex:** ☐ Female ☐ Male (ineligible)

Hospital Number: ..... **N.H.S. Number:** .....

G.P.s Name: .....

G.P.s Address: .....

Current Menopausal Status: ☐ Pre ☐ Peri ☐ Post ☐ Not Known

History of other primary or contralateral cancer: ☐ Yes ☐ No ☐ Not Known

If yes, date diagnosed: ☐☐/☐☐ (Month/Year) **Site of cancer:** .....

Surgery Details:

Consultant Surgeon: ..... Date of Surgery: ☐☐/☐☐ (Month/Year)

Final Surgical Outcome: ☐ Lumpectomy ☐ W.L.E. ☐ Mastectomy

Tumour Completely Removed: ☐ Yes ☐ No (ineligible) Free from Distant Metastases: ☐ Yes ☐ No (ineligible)

Histology Details:

Maximum Tumour Size: ☐☐.☐ cm ☐ Not Known

Histological Grade: ☐ 1 (Well diff) ☐ 2 (Mod diff) ☐ 3 (Poorly diff) ☐ Not Known

Histological Type: ☐ Ductal ☐ Lobular ☐ DCIS ☐ Not Known ☐ Other: .....

Lymph Nodes: ☐ -VE ☐ +VE ☐ Not Known ER Status: ☐ -VE ☐ +VE ☐ Not Known

Treatment Details:

Other Adjuvant Treatment: ☐ Radiotherapy ☐ Chemotherapy ☐ Ovarian Suppression ☐ None

Tamoxifen Started: ☐☐/☐☐ (Month/Year) Dose: ☐☐ mg per day

Duration of Tamoxifen before randomisation (min. 2 years): ☐☐ years

aTTom Study Number: ☐☐☐☐☐☐☐

Randomisation Details: Before randomisation, check eligibility criteria on the aTTom randomisation checklist.

Date of randomisation: ☐☐/☐☐/☐☐☐☐ (Day/Month/Year) Patient randomised to: ☐ STOP NOW ☐ CONTINUE for 5 years

APPENDIX II

Registration and Randomisation Checklist

Adjuvant Tamoxifen Treatment - Offer More?

REGISTRATION AND RANDOMISATION CHECKLIST

For IMMEDIATE Randomisation, call

0800 371 969 *or* 0800 731 7625

- To register a patient, complete the registration form and either call the number above, or fax the form to 0800 731 7625: we will then write to tell you the patient's study number.
- When you randomise a previously registered patient, it will speed up randomisation if you give the patient's study number. This number was allocated at registration and should be on the registration form. It will also assist us if you could tell us the patient's N.H.S. number, if you have not already done so.
- Before randomising, please check the following eligibility criteria:

  - The patient has given informed consent
  - The patient is still taking tamoxifen
  - The patient is well and free from relapse

  If any of these criteria are not satisfied, the patient is no longer eligible for randomisation.
- Randomised patients will be allocated to either stop treatment or to continue tamoxifen for a further 5 years.
- After registration or randomisation, we will write to you confirming the patient's details, and, if randomised, we will send a letter to the patient's G.P. informing them of the outcome of the randomisation.

APPENDIX III

aTTom Patient Information

This is an example of a patient information sheet. Where appropriate the aTTom co-ordinators will be happy to amend this to meet participants individual requirements, or those of the Local Research and Ethics Committee.

aTTom Study Patient Information

aTTom*:- adjuvant Tamoxifen Treatment - offer more?*

Over a million women worldwide are taking tamoxifen after surgery for breast cancer. Research has shown that this reduces the risk of their breast cancer returning. But what we do not know is:

How long should women carry on taking tamoxifen?

The aim of the aTTom study is to answer this important question and with your help we can do this.

At the moment different doctors give different treatments. Some women take tamoxifen for 2 years, some for 5 years and some for even longer.

Sometimes there are definite reasons why women should carry on taking tamoxifen after surgery and sometimes there are definite reasons why they should stop. But for most women a time eventually comes when her doctor is not sure whether or not she should continue treatment. It is at this time that your doctor will invite you to take part in the aTTom study.

aTTom is a national study in which doctors throughout the UK are taking part. It includes women like you who have been taking tamoxifen for some time and are unsure whether or not they should continue. Half of the women who agree to take part in the study will be asked to continue taking tamoxifen for at least another five years and the other half will be asked to stop taking tamoxifen. This is the only way that we can find out for sure exactly how long women should take tamoxifen.

Tamoxifen - the benefits and risks

We know that taking tamoxifen for a few years saves a lot of lives, but there is not yet enough experience with this drug to be sure about the additional risks and benefits of taking tamoxifen for longer.

The possible benefits of longer tamoxifen are:

- Less risk of your breast cancer returning.
- Less risk of a new cancer in your other breast.
- Tamoxifen reduces the level of cholesterol in the blood which may prevent heart attacks.
- Tamoxifen helps to protect the skeleton from osteoporosis (which weakens bones).

Tamoxifen causes few serious side effects. Some women suffer minor side effects which include menopausal symptoms, slight hair loss, stomach upsets and skin rashes. Generally, women find that these lessen as treatment continues and cease altogether when treatment is stopped. You will have been taking tamoxifen for some time and will already know how it affects you.

More serious risks from longer term tamoxifen that we do not yet know enough about are:

- There is a small increase in the risk of developing cancer of the womb (endometrial cancer) for women who take tamoxifen. Endometrial cancer can nearly always be successfully treated because it has a reliable early warning sign of vaginal bleeding. Also, we do know that a few years of tamoxifen has prevented many more breast cancers, than it has caused endometrial cancers.
- Eye problems have sometimes been reported with tamoxifen and a rare complication called 'tamoxifen retinopathy' can cause eyesight problems (which usually disappear when treatment is stopped).
- There is also a very small increase in the risk of developing blood clots (thromboembolism).

These risks are small but they are likely to increase the longer tamoxifen is taken. This is one of the things we need to know more about. Our hope is that the benefits from carrying on taking tamoxifen will continue to outweigh the risks.

The reason we are running the aTTom study is to find out exactly how long women with breast cancer should carry on taking tamoxifen so that they get the most benefit and least risk. This is why we are inviting many thousands of women to take part.

Entering the aTTom Study

If you agree to take part your doctor will phone the study office to enter you into the study. The study office will ask your doctor for some details about you and your disease and will then tell your doctor whether you should stop or continue tamoxifen.

Neither the women who take part in aTTom, nor their doctors, will know in advance whether they will be asked to continue taking tamoxifen (for at least another five years) or to stop. The decision is made at random at the study office. This is so that at the end of the trial, the two groups that we are comparing are the same, and we can trust the study results.

You do not have to take part in aTTom if you don't want to and you do not need to give a reason for this. If you do join the study and later change your mind you are free to leave and, again, you do not have to give a reason. Whatever you decide, you will still receive the best level of care from your doctor.

Patient Confidentiality

If you do agree to take part in aTTom, simple information about your progress will be provided each year, in confidence, by your own doctor to the study office. This information will be treated in strict confidence, in the same way as your other medical records. Neither you, nor any other patients in the study will be identified when the results are reported.

More Information

If you would like more information about **aTTom** either ask a member of your breast care team (see below) or write to:

The **aTTom** Study Office • CRC Trials Unit • Institute for Cancer Studies
Vincent Road • Edgbaston • Birmingham B15 2TT.

Further information on breast cancer treatment can also be obtained from the British Association of Cancer United Patients and their families and friends (BACUP) on Freephone 0800 181199

Local Contact:..... Tel:.....

APPENDIX IV

Annual Follow-up Form

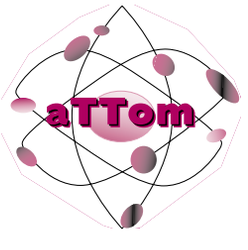
The following information will be requested at yearly intervals. For patients who no longer attend hospital clinics regularly (or on request), follow-up information will be obtained from the patient's GP. On completion the form may be faxed to the study office on 0121-414-3700 or returned in the free post envelope.

aTTom ANNUAL FOLLOW-UP

Doctors Name: ..... **Address:** .....

Name of patient, date of birth, hospital number	Name of patient, date of birth, hospital number	Name of patient, date of birth, hospital number	Name of patient, date of birth, hospital number
Joanna Smith 04.03.38 G123456			
Date of surgery	**Date of surgery**	**Date of surgery**	**Date of surgery**
15.03.89			
Date of randomisation	**Date of randomisation**	**Date of randomisation**	**Date of randomisation**
09.10.94			
This patient was randomised to:	**This patient was randomised to:**	**This patient was randomised to:**	**This patient was randomised to:**
STOP			
Is the patient currently taking tamoxifen?	**Is the patient currently taking tamoxifen?**	**Is the patient currently taking tamoxifen?**	**Is the patient currently taking tamoxifen?**
Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Date and site of first local/loco-regional recurrence	**Date and site of first local/loco-regional recurrence**	**Date and site of first local/loco-regional recurrence**	**Date and site of first local/loco-regional recurrence**
Date and site of first distant recurrence	**Date and site of first distant recurrence**	**Date and site of first distant recurrence**	**Date and site of first distant recurrence**
If patient has died please give date and cause of death	**If patient has died please give date and cause of death**	**If patient has died please give date and cause of death**	**If patient has died please give date and cause of death**
If patient is still alive approx. date last seen	**If patient is still alive approx. date last seen**	**If patient is still alive approx. date last seen**	**If patient is still alive approx. date last seen**
COMMENTS: Please give details of any serious toxicity, any events involving hospital admissions and the name of the Doctor responsible for the patient if they are no longer in your care.	**COMMENTS: Please give details of any serious toxicity, any events involving hospital admissions and the name of the Doctor responsible for the patient if they are no longer in your care.**	**COMMENTS: Please give details of any serious toxicity, any events involving hospital admissions and the name of the Doctor responsible for the patient if they are no longer in your care.**	**COMMENTS: Please give details of any serious toxicity, any events involving hospital admissions and the name of the Doctor responsible for the patient if they are no longer in your care.**

Please Return this form in the enclosed freepost envelope to the aTTom Study Office, CRCTU, Clinical Research Block, Medical School, Birmingham, B15 2TA

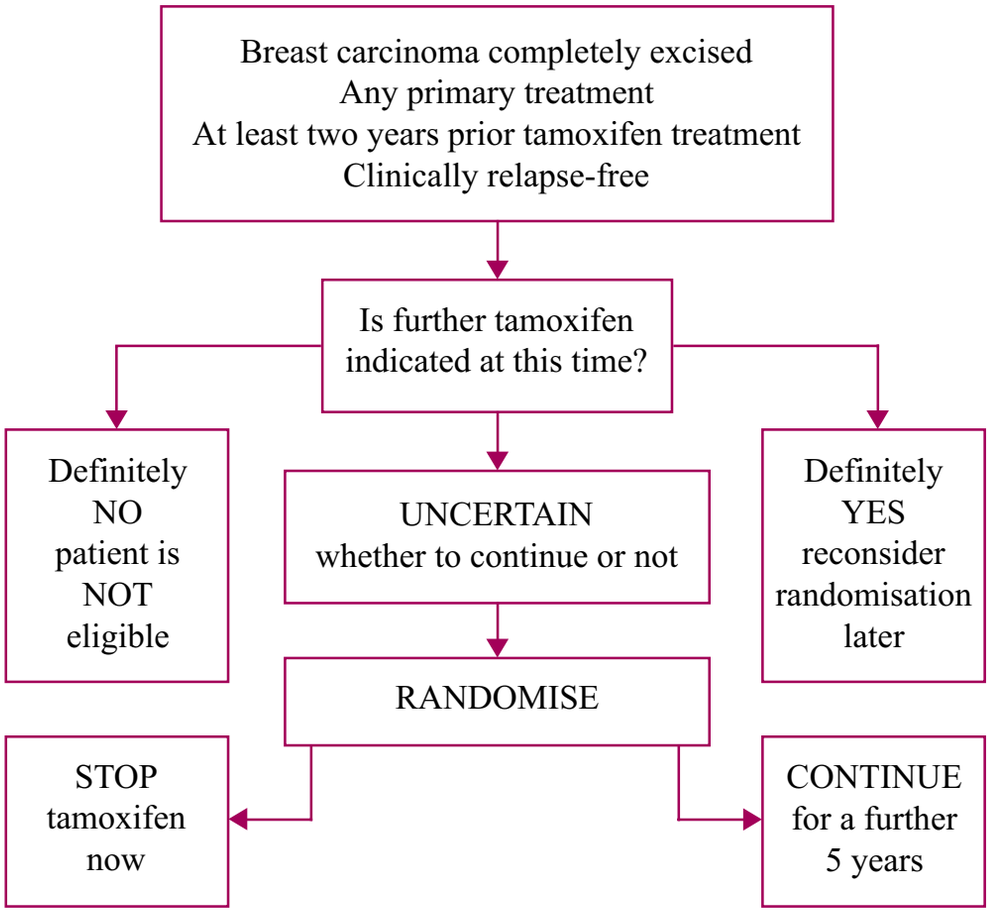


PROTOCOL

aTTom - adjuvant Tamoxifen Treatment offer more?

aTTom is a very large, uniquely simple, randomised study of the effects of prolonging adjuvant tamoxifen treatment on the survival of patients with operable breast cancer.

If you are uncertain about the optimum duration of tamoxifen -
Join the aTTom study today.



RANDOMISATION IS JUST ONE QUICK CALL

FREEPHONE 0800 371 969 or 0800 731 7625

aTTom Study Office

CRC Trials Unit • Institute of Cancer Studies • Vincent Drive • Edgbaston • Birmingham B15 2TT
Tel: (0121) 414 3796 • Fax: (0121) 414 3700 • e-mail: attom@bham.ac.uk
Randomisation Freephone: 0800 371 969 or 0800 731 7625