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World-wide, more than 1 million women with early breast cancer take adjuvant tamoxifen. But, there is substantial uncertainty about the optimal duration of treatment, and in particular, as to whether tamoxifen should be stopped after 5 years, or continued for longer- this has not been addressed adequately in the other small trials of this question. ATLAS is an international trial designed to assess this reliably. If the study demonstrates that longer treatment confers additional benefit, several thousands of deaths could be avoided each year if women are treated accordingly. With funding from the US Army BCRP, a world-wide collaboration has been established. By early 1999, ATLAS will be the largest ever trial of tamoxifen duration. 32 countries are participating, 330 centres have ethics approval, 246 centres are randomizing. By 30/11/1998, 3500 women had entered the study. Accrual should increase as more centres obtain ethics approval and the 10-20,000 accrual target should be reached early in the millenium. 3 follow-up cycles have been undertaken demonstrating good treatment compliance in both study arms, and reliable and complete acquisition of follow-up data. Additional funding is required to maintain the collaboration to achieve the accrual target and long-term follow-up.

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FOREWORD

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Richard Peto 27/10/98

PI - Signature Date

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A. INTRODUCTION

This is the final report to the US Army summarizing the work undertaken on ATLAS (Adjuvant Tamoxifen - Longer Against Shorter), a large international randomized trial of tamoxifen duration in early breast cancer. ATLAS received its initial funding through the US Army Breast Cancer Research Program (**Grant number DAMD 17-94-J-4422**).

Background to ATLAS & summary of progress

The worldwide randomized evidence now shows that a few years of adjuvant tamoxifen, following the initial management of early breast cancer, reduces the risk of relapse and improves long-term survival. Moreover, at least 5 years of tamoxifen reduces the risk of relapse and may also improve long-term survival[1] to a greater extent compared with shorter regimens. However, there is substantial uncertainty as to whether more than 5 years of hormonal treatment produces additional benefit[2].

ATLAS is designed to assess reliably the balance of benefits and risks of prolonging adjuvant tamoxifen by an extra 5 years in women for whom, after a few years of treatment, there is uncertainty as to whether they should stop their tamoxifen now, or continue for several years longer. This is of relevance not only to women who receive tamoxifen, but also to the appropriate duration of use of other hormonal therapy. About 10-20 000 eligible women are to be randomized in ATLAS either to stopping their tamoxifen, or continuing it for 5 more years and then followed for at least 10 years to allow sufficient time for the overall balance of benefits and hazards to emerge.

With the US Army funding, major progress has been made towards fulfilling the primary objective of the ATLAS trial. Under the direction of the coordinating centre (i.e. Oxford Clinical Trial Service Unit), an international network of clinicians has been established - 335 centres now have ethics approval, and 246 of these are actively entering women into the study. 3500 women have been randomized by the end of November 1998, and in several countries, accrual rates are increasing rapidly. Moreover, if, as seems likely to be the case by the end of the year 2000, a general consensus emerges through the Early Breast Cancer Trialists Collaborative Group (EBCTCG) that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, the question of whether 10 years is better than 5 years will become even more pertinent, and this is likely to stimulate further interest in ATLAS (and thus increase accrual). Even so, by early 1999, ATLAS will be the largest ever trial of tamoxifen duration - but more importantly, the study is now well on its way to establishing whether prolonging tamoxifen beyond the first 5 years provides additional benefit - a question that has not been addressed adequately in the other small trials of 5 versus 10 years of tamoxifen. It is anticipated that the accrual target will be reached in the early years of the next millenium. Following the randomization of 10-20,000 women, they will need to be followed up for many years (i.e. at least until 2005 and preferably until 2010) until a clear answer emerges. Procedures are now in place for ensuring reliable long-term follow-up of women randomized, and the annual follow-up cycles conducted so far have demonstrated their feasibility in terms both of acceptability (from a workload perspective) to clinicians and of completeness of data. Compliance with allocated study treatment is good in both arms of the study.

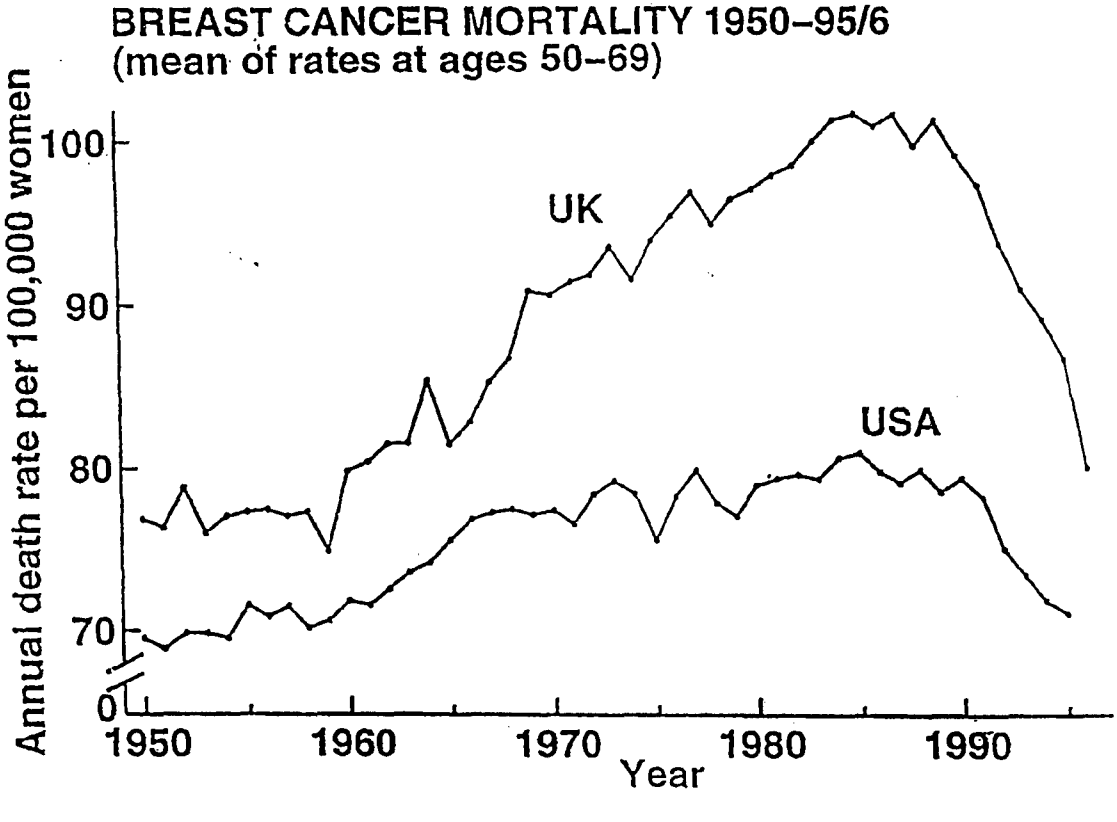
With US Army funding, the prospect of international collaboration on a massive scale is now a reality. The importance of ATLAS is widely recognized by collaborators, and the pragmatic design of the trial — with emphasis on streamlined procedures and minimal workload for collaborators — makes large-scale participation practicable, and has helped to overcome the difficulties in organizing this international collaboration. However, to maintain the collaboration to achieve the accrual target and long-term follow-up, additional funding is needed. Funding has been obtained from other sources, but continued funding from the US Army Breast Cancer Research Program is still needed to ensure the success of the study, and is now requested as part of the Final Report.

The currently randomized evidence on adjuvant tamoxifen

Breast cancer is common with more than 800 000 new cases diagnosed annually worldwide. It is the leading cause of female neoplastic death in most developed countries; and, in developing societies, breast cancer is only second to cervical cancer in cancer deaths. The reliable demonstration that a practicable and widely available treatment for such a common disease produces a moderate improvement in long-term survival (e.g. improving survival by a few per cent from, say, 50% to 52 or 53%) could lead to the treatment of some hundreds of thousands of women, and the consequent delay of several thousand deaths worldwide, each year.

Following the demonstration by the EBCTCG meta-analysis in the mid-1980s that tamoxifen confers definite survival benefits[3], there was a substantial increase in the use of tamoxifen. The value of tamoxifen has been confirmed in subsequent meta-analyses by the EBCTCG[1,3,4]; more than one million women worldwide are currently prescribed tamoxifen. This makes it one of the most widely used and effective forms of medical oncology, preventing tens of thousands of breast cancer deaths each year worldwide. Before the EBCTCG results emerged, there had been little evidence of any decrease in breast cancer death rates over the previous half-century. But now, at least in those countries where tamoxifen is being widely used amongst women who stand to benefit, a sudden decrease in breast cancer mortality is being observed during the early 1990s, which can be attributed largely to the benefits of improved treatment, particularly with tamoxifen[5-6] (Figure 1).

Figure 1: Breast cancer mortality in England and Wales, 1950-96[6]

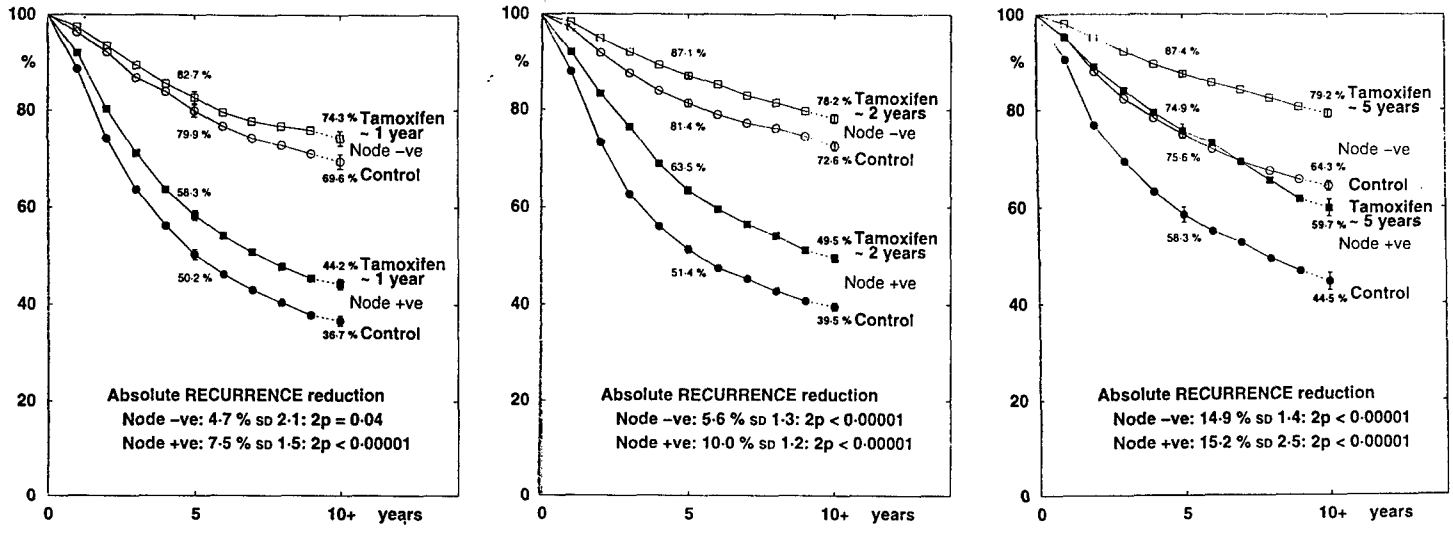


The most recent EBCTCG meta-analysis of 55 randomized trials of adjuvant tamoxifen allowed much more detailed conclusions to be drawn regarding effectiveness[1] (Appendix 1). It demonstrated, for women with oestrogen receptor (ER) positive disease and for those with no ER assay available, a highly significant improvement in 10-year survival corresponding to an average of about 5 or 6 fewer deaths per 100 women treated with about 5 years of tamoxifen regardless of age or nodal status. A number of questions remain unanswered, however, regarding the optimal use of tamoxifen - for example, in relation to duration - if this uncertainty is to be resolved, further large-scale further randomized evidence is needed in trials comparing - within the same study - longer versus shorter tamoxifen regimens[1,2,7].

The relevance of tamoxifen duration

5 years vs. 1 or 2 years: For recurrence prevention, longer is better: The EBCTCG has so far reviewed only trials of tamoxifen versus no tamoxifen and then amongst these trials, has investigated the relevance of duration. Most trials of tamoxifen have involved 1, 2 or 5 years of tamoxifen vs. no tamoxifen. Within this range, longer tamoxifen regimens seem more effective at preventing or delaying recurrent disease and may also improve long-term survival compared with shorter regimens (Figure 2).

Figure 2: Trials of 1 year, 2 years, 5 years of tamoxifen, vs. no tamoxifen: Absolute risk reductions in recurrence during the first 10 years amongst women with potentially hormone-sensitive disease, subdivided by tamoxifen duration and nodal status[1]



A second generation of trials comparing 2 years versus generally about 5 years of tamoxifen has been started. These trials should eventually provide reliable evidence on the relative effects of a few extra years of treatment. Preliminary results from such comparisons support the indirect evidence from the EBCTCG overview that, at least for recurrence, longer treatment is more effective[8-9]. A recently reported trial conducted in France comparing 2 years of tamoxifen with about 7 years produced the same finding, with women who had received longer treatment having significantly reduced rates of recurrent disease[10]. However, it will take many years for these relatively small trials to provide a reliable answer in particular with respect to overall survival, and further randomization will produce an answer more rapidly. Thus, in the interim, it remains appropriate to supplement these preliminary data with evidence from other ongoing trials, including ATLAS, addressing the question of duration. The EBCTCG will be reviewing these trials of 2 years of tamoxifen versus longer in the year 2000 and if this shows that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, the question of whether 10 years is better than 5 years will become even more pertinent, and will eventually have to be answered.

5 years versus longer: Still unanswered for recurrence and survival (Appendix 2): So far, the net effect of tamoxifen when used for longer than 5 years has not been properly studied either through indirect comparisons of duration between trials of tamoxifen versus no tamoxifen, or through direct comparisons in trials which compare within the same study, 5 years of tamoxifen versus longer treatment. Concerns have been expressed about tamoxifen resistance[11] with more prolonged treatment, but the mechanisms of resistance are poorly understood and more importantly, so far, this has not been supported by randomized evidence. The current trials are of insufficient size - even in combination (they have recruited just 1700 patients) - to detect the type of moderately sized difference that might exist[11-13]. The three (ECOG, Scottish Cancer Trial and NSABP B-14) directly randomized comparisons that started long enough ago to have produced some results, have now closed. All three involved only small numbers of breast cancer recurrences or deaths after year 5. (For example, in the recent update of the NSABP B-14 trial of 5 versus 10 years of

tamoxifen, the total numbers of local, contralateral or distant recurrences after year 5 were only 21 versus 34, respectively, which does not preclude longer treatment being better). It remains quite possible, based on the current evidence available to hope for additional benefit from longer treatment. But, if this is going to be reliably demonstrated, tens of thousands of women may need to be randomized and followed up for at least 10 years. It will probably not be until 2005 or more likely 2010, that there will be sufficient randomized evidence on 5 vs. 10 years of tamoxifen for review by the EBCTCG.

The major deficiency in research evidence and hence, the main uncertainty in clinical practice, lies in the assessment of the effects of prolonging adjuvant tamoxifen beyond 5 years[1,2,7]. The fundamental rationale for the ATLAS trial at the time of the original funding application was to address this uncertainty, and it remains appropriate now: for, ATLAS may be the only trial which is large enough to address this question reliably. (The need for further large-scale randomized evidence on this question and the importance of ATLAS were endorsed by an independent expert Scientific Panel appointed by the US Army in July 1996* in an interim review of the study and the Panel also approved fully the continuing appropriateness of the study in terms of its design and implementation.)

Important long-term side-effects of tamoxifen and the relevance of duration

Tamoxifen reduces the incidence of contralateral breast cancer (i.e. secondary prevention) and this effect appears to be more marked with longer treatment[1]. Although no other long-term beneficial side-effects have yet been reliably demonstrated, long-term use of tamoxifen may also have a beneficial effect on coronary heart disease by lowering cholesterol[19–22] and on osteoporosis through its oestrogen effects[21-24]. While the benefits of tamoxifen are greater with more prolonged therapy, the reliably established adverse long-term side effects may also be affected by the length of treatment. Specifically, the risk of tamoxifen-induced endometrial cancer appears to be increased with more prolonged therapy[1,25-27] and there is a small increased risk of death from thrombo-embolic disease with one extra death from pulmonary embolus per 1000 women treated with about 5 years of tamoxifen[1]. No other major life-threatening or life-prolonging side effects have, as yet, been reliably demonstrated[28-32].

Although an increase in endometrial cancer and thrombo-embolic events attributable to tamoxifen seems definite, this is smaller than the definite decrease in contralateral breast cancer. Moreover, the increase in the number of such deaths is much smaller than the absolute decrease in all-cause mortality. For every 1000 women treated with ~5 years of tamoxifen, about 80 breast cancer deaths will be avoided, compared with 2 extra deaths from endometrial cancer and 1 extra death from pulmonary embolus i.e. in terms of overall mortality, tamoxifen is doing about 30 times more good than harm[1]. Hence, the available randomized evidence when considered in its entirety supports the continued use of tamoxifen in the adjuvant setting[33].

However, both adverse and beneficial effects may increase if tamoxifen is taken for many years, and any assessment of the effects of tamoxifen must address the overall balance of risks and benefits.

Uncertainty leads to variation in clinical practice

The uncertainty concerning the optimal duration of adjuvant tamoxifen has resulted in widespread variation in clinical practice (Figure 3). The ATLAS coordinators have conducted an international survey of tamoxifen prescribing practice (Appendix 3)[34]. Clinicians were sent a postal questionnaire asking whether they routinely used tamoxifen, those factors that influenced usage and the duration of tamoxifen routinely prescribed for different categories of patients with early breast cancer.

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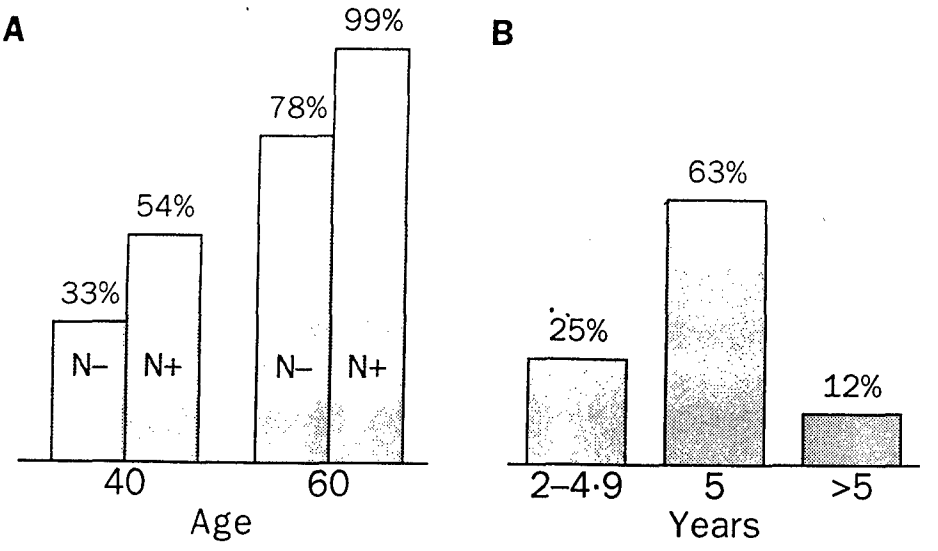
* **Membership:** Professor J Crowley and Professor J Glick (co-chairs); Dr M Abeloff; Dr W T Creasman; Dr E Gehan; Dr S George; Dr R Gelman; Dr B E Henderson; Dr S M Love; Dr M Markman; Dr F Muggia; Dr D Schapira; Dr P A Barr; Dr M A Sestili.

Figure 3: Percentage of clinicians saying they would use tamoxifen, by age, nodal status & duration[34]



Patterns of adjuvant tamoxifen use

A: Effect of age and lymph-node involvement on percentage of breast-cancer doctors who would routinely consider adjuvant tamoxifen.
B: Usual duration of any adjuvant tamoxifen (percentage of doctors, not patients).

The survey showed major variation in the way clinicians use tamoxifen with age and nodal status being key factors influencing use. Additionally, there was substantial variation in the length of tamoxifen prescribed, but about 60% would regularly prescribe tamoxifen for about 5 years. Some routinely used tamoxifen for more than 5 years, suggesting that amongst opinion leaders, some hoped for additional benefit with longer treatment. This hope may be justified but such treatment continuation requires reliable assessment. It is anticipated that the latest EBCTCG findings should result in wider use of tamoxifen in younger women and in those with node negative disease, but the question of duration is still unanswered.

Why does ATLAS need to be so large and to have prolonged follow-up?

The reliable demonstration, or refutation, of any plausibly moderate-sized additional advantage that might be produced from longer treatment requires large-scale randomized comparisons. Small-scale randomized evidence carries the substantial risk of undue weight being given to favourable or unfavourable random fluctuations based on few events — particularly if interim analyses are carried out repeatedly and any extreme "zigs" or "zags" produced by chance unduly emphasized[35]. Long follow-up among a large number of randomized patients is required before sufficient numbers of recurrences and deaths will have occurred to allow reliable comparisons.

But, there is another reason why comparisons of different tamoxifen durations require long follow-up. It is evident from the EBCTCG overview that there is a substantial "carry-over" benefit from tamoxifen lasting beyond the treatment period[1]. A few years of adjuvant tamoxifen produces a reduction in the annual recurrence rate and in the annual death rate not only **during** treatment, but also for a few years **after** treatment has stopped. This persistent benefit **enhanced** the absolute difference in 10-year survival observed in trials of tamoxifen vs. no tamoxifen. However, in trials comparing stopping after a few years versus continuing for longer, this carry-over benefit amongst patients stopping their tamoxifen may mean that, for the first few years of additional treatment, there is little apparent additional benefit from continuing tamoxifen — **even if, later on, a worthwhile benefit from longer treatment emerges.** Consequently, it is imperative that follow-up in such trials is sufficiently long to allow any late survival benefit from continuing tamoxifen to emerge.

Table 1: Example of the numbers of deaths that might be observed in various periods after randomization of 20 000 women between stop and continue tamoxifen after an initial 5 years of tamoxifen

Years since randomization	SHORTER (e.g. stop after ~ 5 years of tamoxifen): 10 000 women	LONGER (e.g. continue for 5 extra years after 5 years of tamoxifen): 10 000 women	Statistical significance of such a result NS = not significant
0-3 years	**~1000**	**~1000**	**NS**
0-6 years	**~2000**	**~1900**	**NS**
0-10 years	**~3000**	**~2750**	**P<0.0001**

The effect size might be larger than this: if it is, then it may be clearer earlier on.

B. BODY OF THE REPORT

Review of statement of work

The initial funding from the US Army has successfully established the infrastructure for this international collaboration, and supported the early stages of the trial's implementation. The first stage of ATLAS has now mainly been completed — that is, the development of a wide-scale collaborative group and the establishment of the materials and procedures needed for the smooth conduct of the trial (details of the central administration of the trial can be found at Appendix 4). But these largely administrative activities have now been translated into actual accrual of patients and their follow-up within ATLAS. ATLAS has now (by the end of November 1998) recruited 3500 women and successfully completed two annual follow-ups on women in the study. By the end of 1998, ATLAS will be the largest trial undertaken of tamoxifen duration, but needs to continue accrual for the next few years to reach its target of between 10-20,000 women and to follow them up long-term.

Statement of Work

October 1994	Finalization of trial protocol
August 1995- October 1996	Identification of national coordinators Establish national network of centres Arrange practicalities of organizing the trial in different countries Develop trial materials for local use Launch meetings in different countries
July/January (annually)	Produce 6-monthly Newsletters for collaborators
Spring (annually)	Interim report to Data Monitoring Committee
Autumn (annually)	ATLAS Steering Committee meeting
Recruitment period	- see estimates below

Year	Current accrual rates continued (A)	Increased accrual following completion in 2000 of shift in standard length of tamoxifen regimen from 2 to 5 years (B)	Increased accrual from B plus increased accrual following the next cycle of the EBCTCG (C)
1996-early millenium			
Dec 1996	**<1000**	-	-
Dec 1997	**~2000**	-	-
Estimated			
Dec 1998	**~3700**	-	-
Dec 1999	**~5500**	-	-
Dec 2000	**~6500**	**~7,000**	**~8,000**
Dec 2001	**~8000**	**~9,000**	**~10,000**
Dec 2002	**~10,000**	**~11,000**	**~13,500**
Dec 2003	**~11,500**	**~13,500**	**~17,000**
Dec 2004	**~13,500**	**~16,500**	**20,000+**
Dec 2005	**~15,000**	**~18,000**	-

(Also, see figure below, page)

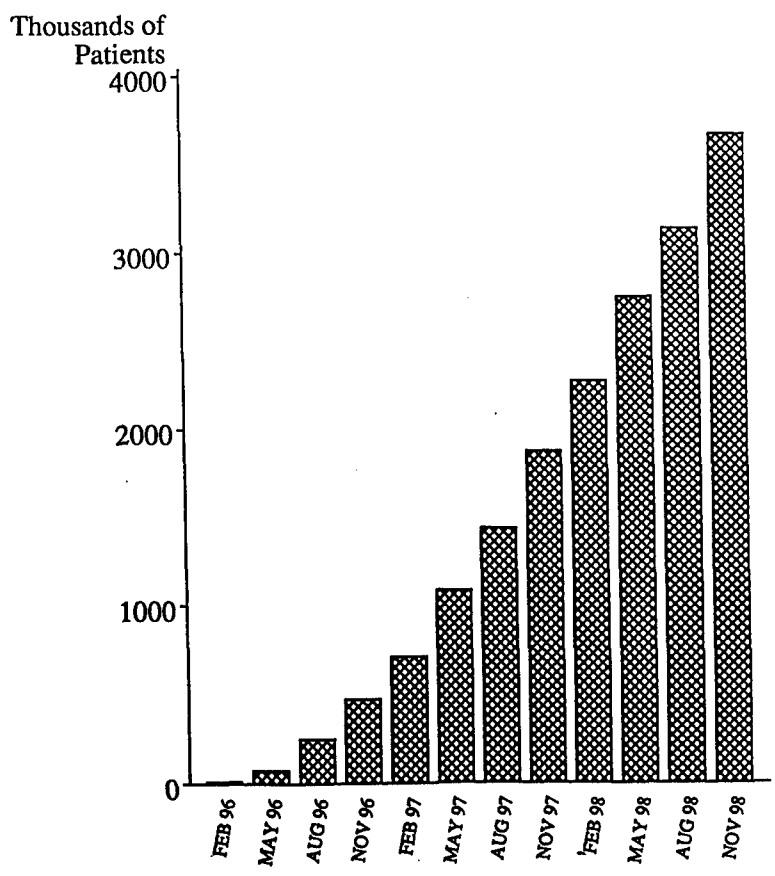
September 2000	Next cycle of EBCTCG and linked ATLAS collaborators' meeting
2005 onwards annually	Follow-up of all women randomized

Status of the ATLAS collaboration

At 30 November 1998 -

- **335 centres with ethics approval**
- **246 centres actively randomizing in 32 countries**
- **3500 women randomized**
- **2 cycles of annual follow-up completed**
- **New centres in Italy and Spain about to start**
- **Current accrual rate should continue to increase**
- **Significantly increased accrual anticipated in 2000**

Figure 4: Global cumulative accrual to ATLAS



Setting up the collaborative network

The first phase of the implementation of ATLAS involved establishing contacts with clinicians worldwide who could work with the international coordinating centre in Oxford to establish a network of clinicians nationally to participate in ATLAS. A list of National Coordinators is at Appendix 4. The major effort has been undertaken by R Peto and C Davies who have travelled worldwide to establish such contacts and to raise the profile of the trial at breast cancer meetings, both those set up specifically for ATLAS, and as part of general breast cancer meetings.

ATLAS PRESENTATIONS AT SCIENTIFIC MEETINGS

(EXCLUDING PRESENTATIONS AT MEETINGS SET UP SPECIFICALLY FOR ATLAS)

1st European Breast Cancer Conference - Florence - September 1998
Early Breast Cancer: How long should tamoxifen continue?
C Davies, H Monaghan, R Peto

XI Congreso Ibero-Latinoamericano - Pucon, Chile April 1998
Early breast cancer: World-wide meta-analysis of randomised trials

20th Annual San Antonio Breast Cancer Conference October 1997
ATLAS:an international trial of tamoxifen duration
Davies C Peto R

US Army: Era of Hope Meeting Washington DC November 1997
ATLAS:an international trial of tamoxifen duration
Davies C Peto R

7th International Congress on Annual Cancer Treatment - Paris February 1997
ATLAS: An international megatrial of tamoxifen duration in early breast cancer
Davies C Peto R Gray R

3rd Portuguese-Brazilian Mastology Congress - Recife, Brazil November 1996
ATLAS: An international trial of tamoxifen duration
Davies C Peto R

Australia-New Zealand Breast Cancer Trials Group: Annual Scientific meetings 1996 and 1997
The randomised evidence on adjuvant tamoxifen and the ATLAS trial
Davies C

More than 30 meetings have been organised in different countries worldwide specifically for ATLAS.

Many of the countries in which ATLAS is taking place did not have an existing trial network that could be readily exploited, although where these were available (for example, in Italy and Australia) ATLAS has been integrated into them. Furthermore, although there tended to be an established trial coordinating office with which to work in those countries where there was already a network, in other countries it has been necessary — after establishing a network — to develop mechanisms for coordination of this newly-developed network.

Maintaining and strengthening the ATLAS collaboration

Once this initial step had been taken, the next phase in the trial was and remains to maintain, strengthen and extend the collaboration within each country, and to ensure active participation in ATLAS. In view of the scale of the collaboration, this has been achieved mainly through close collaboration between Oxford and each of the national coordinators, who are then responsible for coordinating the clinical network in each of their respective countries. The international coordinating centre still undertakes the bulk of the

administrative workload and has overall responsibility for coordination and management of the trial. However, Oxford is dependent on the support of the various national coordinators, each of whom is a member of the ATLAS Steering Committee.

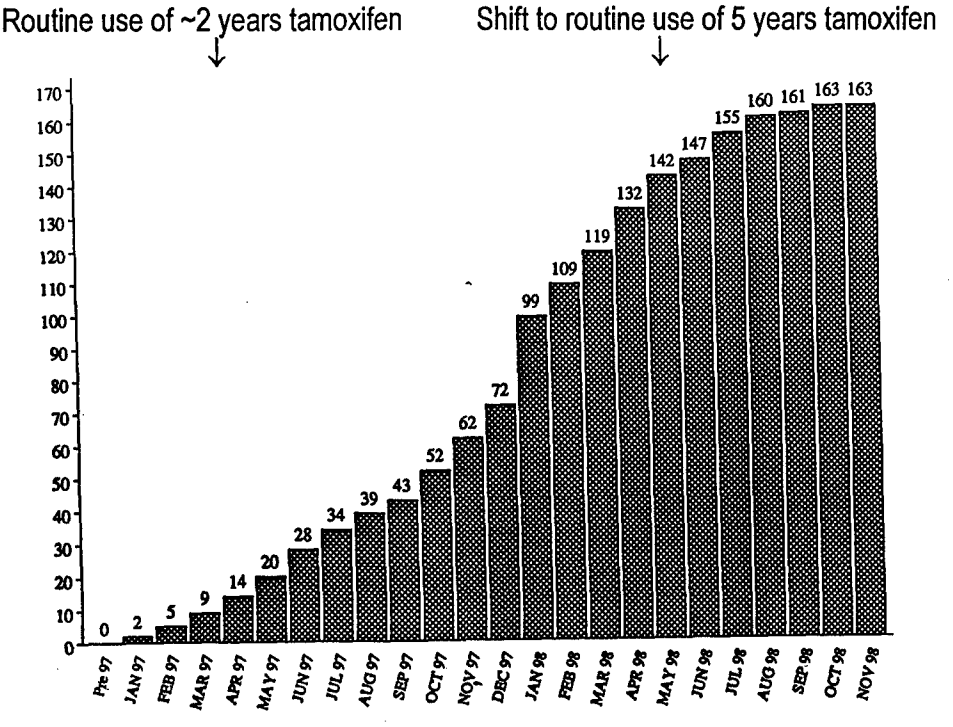
Current global accrual

	November 1996	November 1997	November 1998
Centres with ethics approval	154	253	335
Global accrual	469	1867	3500

No local ethics committee has declined to approve ATLAS and it is anticipated that several hundred hospitals should eventually participate. A letter of invitation to non-collaborating centres currently on our database will be distributed, summarizing the now finalized EBCTCG data on tamoxifen. With the renewed interest in tamoxifen following the publication of both the report by the EBCTCG and also the 3 trials of tamoxifen as a chemopreventive agent in women at high risk of breast cancer, it is anticipated that this mailshot will result in new centres joining the ATLAS collaboration. 237 of the 335 centres with ethics approval are actively randomizing patients into ATLAS with the remainder about to start. Some centres have required a free supply of tamoxifen before being able to accrue patients, whilst others are in the process of implementing the trial locally. In particular, the identification of potentially eligible patients who might be invited to join ATLAS can be time-consuming at the outset of the trial, although once this process is started, it becomes easier and is a more organized approach to accessing the potential pool of patients. Ways to facilitate this process are discussed below (page 13). More than 3500 patients have been randomized by 30 November 1998 and, as additional centres join the collaboration, and as committed centres steadily accrue patients, randomization is expected to continue to increase.

Impact or emerging research evidence on accrual to ATLAS

Patients have been entered into ATLAS at varying points in terms of their prior duration of adjuvant tamoxifen according to the point at which they and their doctors became uncertain about whether to stop or continue their tamoxifen (which is the main eligibility criterion for ATLAS). A few years ago, although there was still uncertainty about the appropriate length of tamoxifen, the majority of doctors would probably have been expected to prescribe about 2 years of tamoxifen routinely. However, now, with the emerging evidence that, at least for recurrence, about 5 years is more beneficial than shorter treatment periods, the situation is changing. There is a general shift in clinical practice towards the use of longer regimens. The impact of this can be seen in accrual rates in some countries participating in ATLAS such as Poland:-



As a result, accrual to ATLAS may take longer than originally anticipated since some clinicians may not become uncertain about the continuation or stoppage of tamoxifen until later, after their patients have received about 5 years of tamoxifen. The use of the uncertainty principle as the main eligibility criterion in ATLAS **embraces** this shift in clinical opinion, allows ATLAS to remain pertinent to the residual uncertainty about tamoxifen, and allows clinicians to address their "updated" uncertainties by offering randomization for those patients for whom there is uncertainty about stopping or continuing **whenever that uncertainty may arise**.

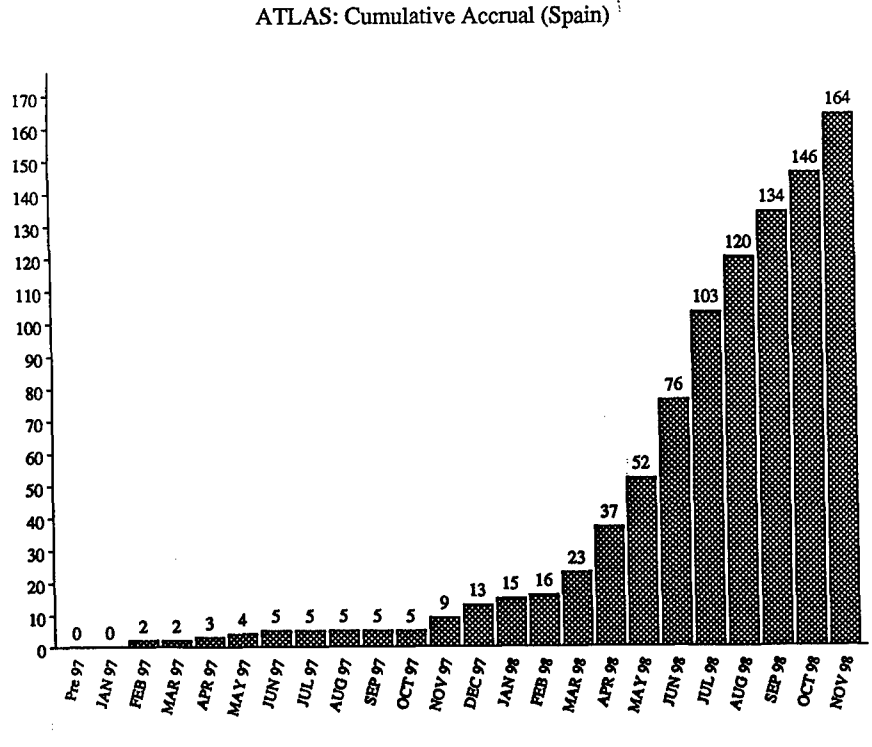
However, efforts are being made to try to increase accrual in those countries where 5 years of tamoxifen has been standard practice for some years now, rather than being recently introduced.

Expanding the collaboration and increasing recruitment

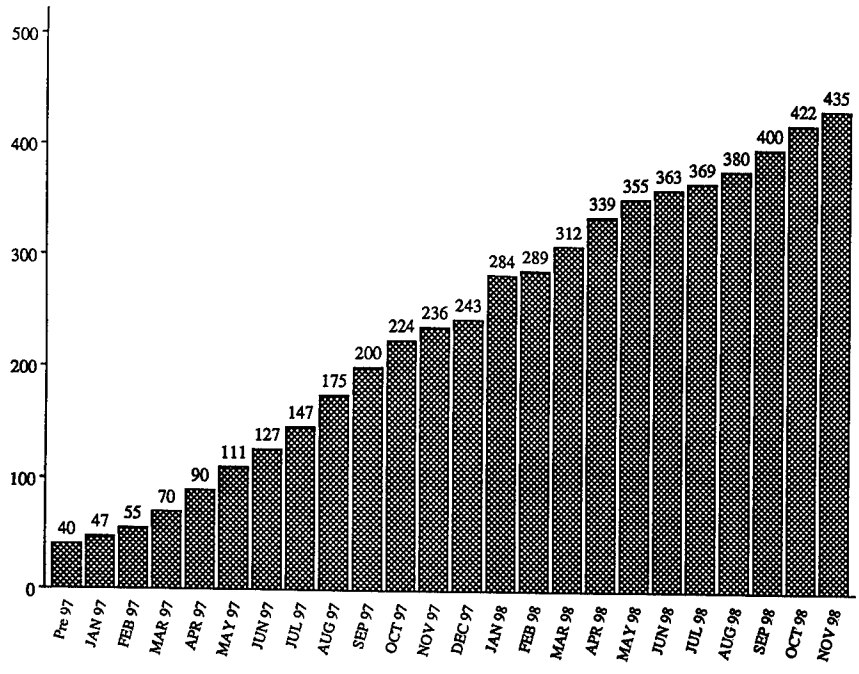
Those countries still expected to make a major contribution to ATLAS in terms of patient accrual, notably, Spain, Argentina and Italy, have had difficulties relating to regulatory authority approval of the trial, importation of free tamoxifen etc. These problems which could not have been anticipated at the outset of the study have now been largely overcome and so again, accrual rates are expected to rise. In particular in Spain, accrual is increasing very rapidly now that the national coordinating centre is functioning effectively and centres are obtaining ethics approval.

ATLAS started in Spain in February 1998. By November 1998, 31 centres were actively randomizing patients into the study with a total of 146 randomized: given that ethics approval takes at least 90 days to obtain, the rate of accrual in Spain is very rapid and is expected to increase. More than 40 centres have ethics approval and this is also expected to increase. In Italy, there are already 16 centres randomizing women into ATLAS, and the national coordinator estimates that this will increase to more than 40 centres now that the administrative problems are resolved. Discussions are still ongoing with leading clinicians in North America regarding the possible implementation of the trial there. Regardless of the involvement of additional countries, ATLAS is now set to achieve its accrual target. Expansion of the collaboration remains appropriate, however, since the larger the collaboration, the more rapid the recruitment target will be reached.

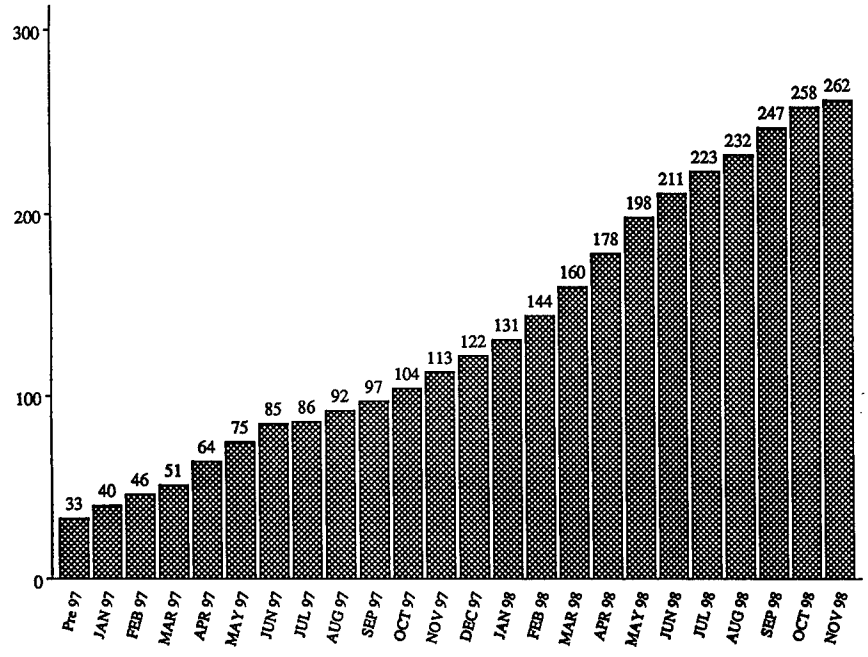
Figure 5: Cumulative accrual in a sample of those countries already making a significant contribution to accrual in ATLAS, and where accrual rates are likely to increase in the next few years



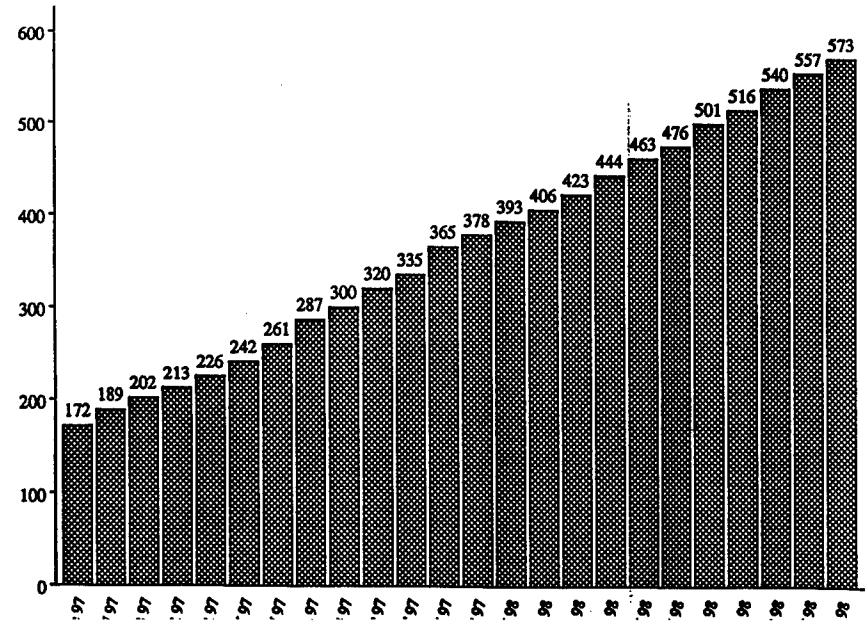
ATLAS: Cumulative Accrual (Chile)



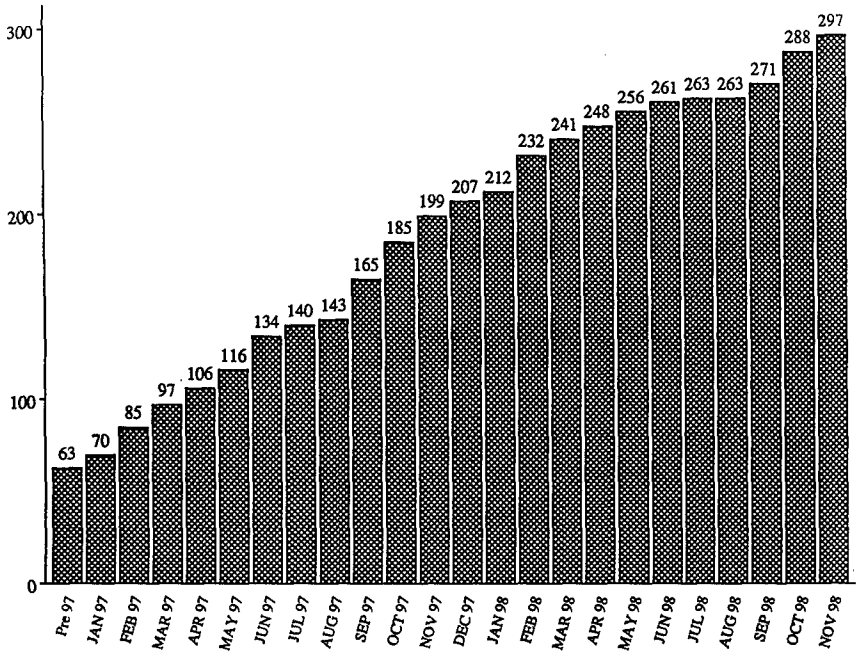
ATLAS: Cumulative Accrual (Argentina)



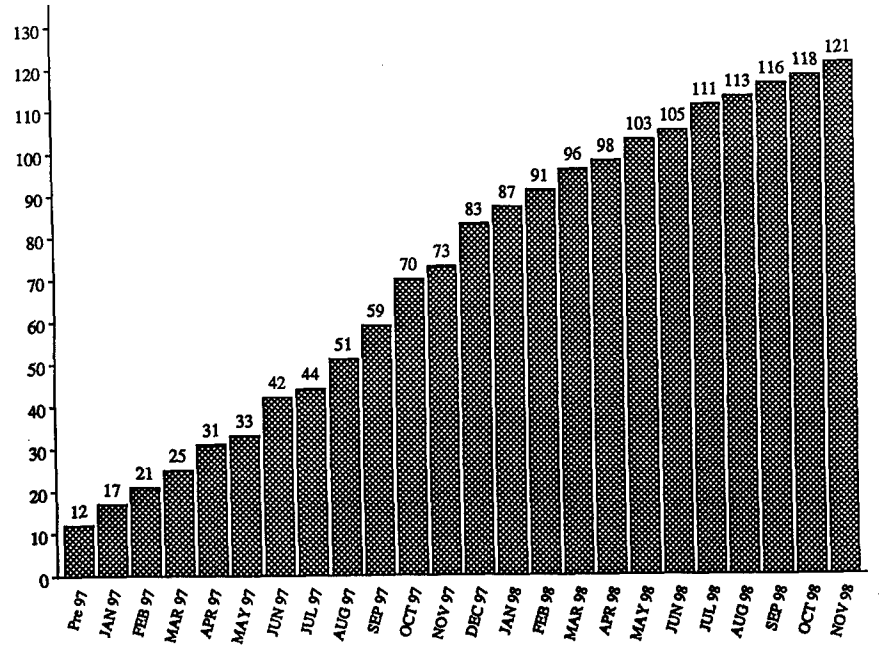
ATLAS: Cumulative Accrual (India)



ATLAS: Cumulative Accrual (Czech Republic)



ATLAS: Cumulative Accrual (Italy)

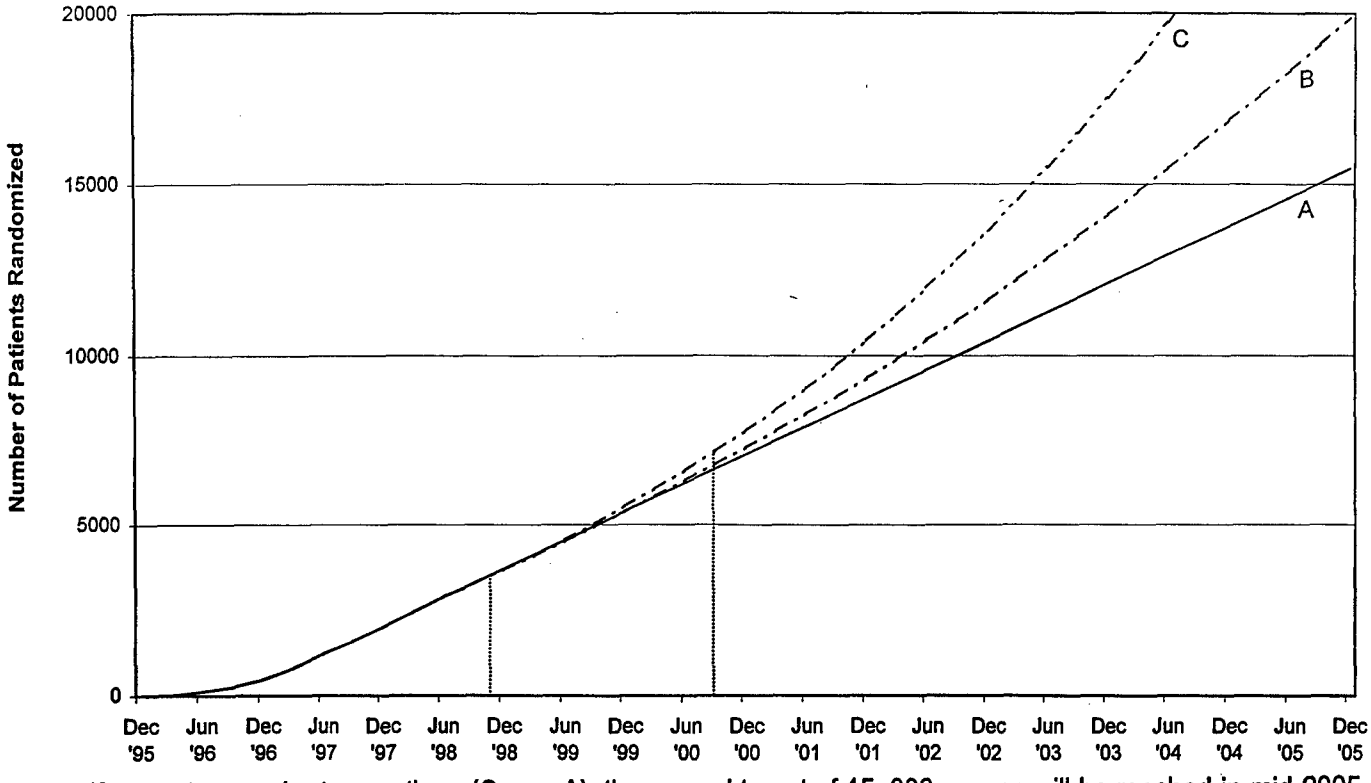


Second randomization into ATLAS

One way to increase accrual to ATLAS is to involve women in ATLAS who are already involved in other breast cancer trials. As stated in the original ATLAS protocol (Appendix 6 page 6), randomizing patients into more than one study does not jeopardize the scientific validity of either study, and allows more than one question to be addressed. In some of the current trials of hormonal therapy, some or all of the women receive about 5 years of such treatment. But among women in such trials reaching their fifth year of hormonal treatment over the next few years, but there will still be uncertainty as to whether to stop or continue such treatment. At this point, those who appear still to be free from disease and who have reliably complied with 5 years of tamoxifen treatment could be re-randomized in ATLAS to stop (unless they later recur) or to continue with five more years of some such treatment. This will help to increase accrual to ATLAS, and also to resolve the clinical dilemma that the clinician faces for that woman about whether to stop or continue with their hormonal therapy. Clinicians involved in such trials are being encouraged to consider their patients for a second randomization into ATLAS. Breast cancer trials not of treatment duration may also be compatible with ATLAS, as long as the patients in those trials are given some years of hormonal treatment. The ABC Trial is one example of such a trial and tests whether adjuvant chemotherapy and/or ovarian suppression add to the benefits of tamoxifen. 20 mg/day tamoxifen is usually prescribed in ABC for 5 years. After 5 years, however, there may well be uncertainty for many women about stopping tamoxifen or continuing for some years longer. These women are eligible for ATLAS. ATLAS is working closely with the ABC Trials Office, and ABC collaborators now have the opportunity to consider randomizing their ABC patients into ATLAS.

Progression of accrual to ATLAS over the next few years and into the millenium

Figure 6:



If current accrual rates continue (**Curve A**), the accrual target of 15, 000 women will be reached in mid-2005. However, we anticipate that two major factors will contribute to increased accrual around the year 2000.

Firstly, the present lag in accrual as clinicians shift to using 5 years of tamoxifen routinely should largely have disappeared by the end of the year 2000 - the latest EBCTCG Overview was published in mid-1998[1] and we would anticipate that by the end of the year 2000/early 2001, many of the women who have been on tamoxifen now for 2 or 3 years will, by then, be ready to be randomized into ATLAS. If this assumption is correct and, if just a proportion of these women is then randomized, cumulative accrual to ATLAS will follow

curve B. Since many of the clinicians in those countries where this shift in practice is occurring are participating in ATLAS, this assumption may well be justified. Moreover, we are encouraging these doctors to register those patients who may become eligible in the next few years with the ATLAS Trial Office so that when they have had about 5 years of tamoxifen, the ATLAS office can remind the clinicians to consider them for ATLAS.

Secondly, the next cycle of the EBCTCG in 2000 is likely to conclude that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, and the question of whether 10 years is better than 5 years will then become even more pertinent. Since the meta-analysis is co-ordinated by this department, we are in contact with those trialists contributing to the EBCTCG who may have an interest in collaborating in ATLAS. These trialists come to Oxford to hear the preliminary results of the meta-analysis and we anticipate therefore that it will stimulate increased interest in ATLAS among EBCTCG collaborators (many of whom are already taking part in ATLAS). For this reason, are planning an ATLAS collaborators' meeting in Oxford at the time of the next EBCTCG meeting. This increased collaboration could boost accrual further so that it then follows **curve C** such that an accrual target of 15, 000 could be reached as early as mid-2003.

Annual follow-up

In ATLAS, long-term follow-up of all randomized patients is fundamental. In view of the varying health care systems, and management patterns and the availability (or not, as the case may be) of national cancer registration/mortality statistics records in collaborating countries, it has been essential to ensure that appropriate mechanisms are in place for long-term follow-up of women randomized in the different countries. Follow-up takes place on 1 January each year when data is requested on all patients randomized up to the previous October so that data are available in time for the annual Data Monitoring Committee meeting. A reminder is sent out in March for unreturned forms, and then the minority of forms not returned is collected throughout the remained of the year. The third annual follow-up will place in January 1999.

	Jan 1997	Jan 1998	Jan 1999
Number of patients on which follow-up data requested	299	1560	3182
% follow-up data collected	100%	89%	-

Doctors are requested to provide the information as soon as possible - because of the simplicity of the data request and the mechanisms in place to ensure follow-up in all patients in all countries, it is anticipated that there will be minimal loss to follow-up. The Data Monitoring Committee for ATLAS reviews the follow-up data annually along with other aspects of the conduct of the trial, and information relevant to the study.

3rd meeting of the ATLAS independent Data Monitoring Committee

The Data Monitoring Committee meets on an annual basis and its terms of reference are set out in the trial protocol (Appendix 5). The Committee held a telephone conference call in March 1998 and reviewed the progress of ATLAS and data from other adjuvant tamoxifen duration studies. The independent ATLAS Data Monitoring Committee confirmed the continued need for ATLAS and concluded in particular that the recent stoppage of one of the trials of 5 years of tamoxifen versus 10 years (NSABP B-14) may well, in time, be shown to have been premature. The Committee was satisfied with the progress of the trial, noting the steady increase in ethics approval and patient accrual. The Committee unanimously approved the continuation of the trial with the present protocol and patient information sheet. The Chairman of the Committee informed Dr Chris Williams (Chairman of the ATLAS Steering Committee) of these conclusions. The Committee will have a teleconference call in April 1999 to review progress and the Chairman will take any interim decisions as appropriate.

2nd ATLAS Steering Committee meeting: Florence September 1998

The ATLAS Steering Committee had its second meeting in Florence on 29 September 1998, when international ATLAS representatives discussed progress. This venue was selected because it was hosting the First European Breast Cancer Conference and many of the ATLAS National Coordinators were attending that conference. In addition, Professor Peto had been invited to present the EBCTCG data on tamoxifen, ovarian ablation, radiotherapy and chemotherapy at the conference. A poster presentation of ATLAS was also made at the conference.

The specific aims of the Steering Committee meeting were as follows:

1. To review the available randomized evidence on tamoxifen and the implications for ATLAS
2. To review the progress of ATLAS: Globally, nationally and locally
3. To consider ways to strengthen the collaboration, maximize accrual & ensure follow-up

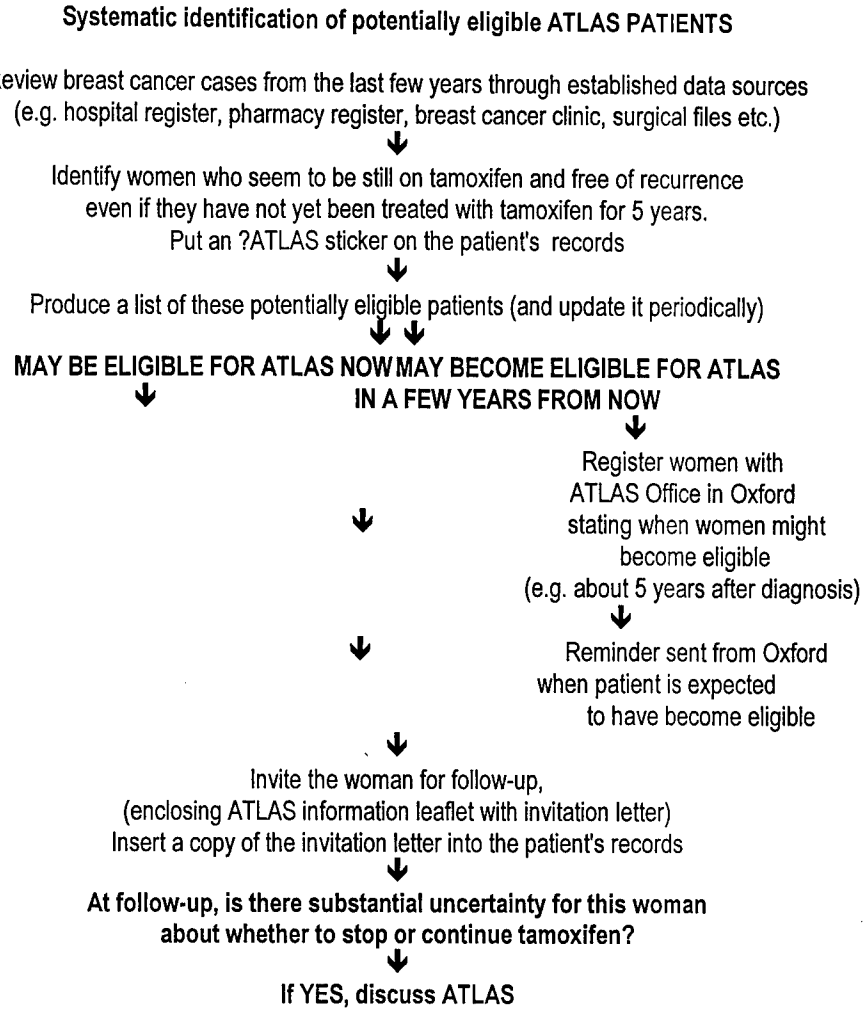
The meeting was constructive. Key issues that were discussed included

- the impact on clinical practice and on ATLAS of the strengthening evidence in favour of 5 years of tamoxifen as a routine minimum. The uncertainty principle would remain as the main eligibility criterion for ATLAS, but it was anticipated that most clinicians would randomize women in ATLAS after an initial 5 years of treatment. The Committee endorsed the DMC recommendation that the trial should continue according to the current design and agreed that the trial materials remained appropriate.

- One difficulty in the trial that has emerged as the trial has progressed is the identification of potentially eligible women, given that they are clinically free from disease and some years away from their original diagnosis. This is compounded by the emerging evidence that most women should probably have received about 5 years of tamoxifen prior to entry to ATLAS, whilst a few years ago, most women might have had just 2 years. In order to identify women more efficiently, a system of registration of women prior to completion of their first five years of tamoxifen and identification of women who might now be eligible for ATLAS might be feasible in some centres (see below). The feasibility and costs of such a system would be explored during the next few months by the ATLAS office in Oxford, and would be piloted.

- It was noted that some centres in each country were recruiting particularly effectively, and these centres would be encouraged to contact up to 5 weaker centres to encourage recruitment. This would strengthen the network in each country as well as increasing the rate of accrual.

- The 2000 EBCTCG Overview, when the results from trials of 2 years of tamoxifen vs. long would be reviewed, would be especially important for ATLAS. Re-launch meetings for the trial would therefore be organized in most countries in September/October/November 2000 when the profile of tamoxifen duration would be high. In the interim, as requested by national coordinators, CD/RP would continue to visit the different collaborating countries to encourage active participation in the study.



C. CONCLUSIONS

Overall, there has been an enthusiastic response to the ATLAS trial worldwide and, with several hundred hospitals in more than 30 countries participating, and with more committed to joining, the possibility of international collaboration on a massive scale is now a reality. By the end of 1998, ATLAS will be the largest trial undertaken of tamoxifen duration and uniquely able to address the question of whether prolonging tamoxifen beyond 5 years is, on balance, beneficial.

The success of the collaboration has been achieved primarily by addressing an important clinical question which is relevant to clinicians worldwide and which is relevant to the management of several hundreds of thousands of women globally. This successful collaboration, because of its strong foundations, will exist not only for the duration of ATLAS but will also provide a "ready-made" international network for future cancer treatment trials. Thus ATLAS can help to establish more widely large-scale streamlined randomized trials that can rapidly provide reliable evidence on questions of public health importance, and promote the adoption of research-based clinical practice globally.

By adopting a scientifically rigorous but pragmatic trial design within ATLAS, widespread collaboration has been facilitated because clinicians can integrate the trial into their routine practice with little or no disruption. The first stage of ATLAS — that is, the development of a wide-scale collaborative group and the establishment of the materials and procedures needed for the smooth conduct of the trial — has now been completed although all of the time, the collaboration is expanding. 335 centres now have ethics approval and this is expected to increase in coming months. 246 of these centres are randomizing patients - the remainder are well on the way now to starting accrual. 3500 patients have already been entered into the trial (by the end of November 1998). Follow-up procedures are practical and reliable data are being collected on more than 90% of patients randomized. As many of the centres in those countries, which are likely to

make an important contribution to the trial, are about to start randomizing, accrual is likely to increase. However, because of the emerging evidence in favour of 5 years as a minimum treatment duration prior to entry to ATLAS, this may slow accrual for the next couple of years and may also make it more difficult to identify potentially eligible women because of the longer time period since their diagnosis. As such, new approaches within ATLAS have been implemented to help clinicians identify women in a more systematic way but maintaining the pragmatic approach within the trial and without creating impractical additional workloads for collaborating clinicians. ATLAS should reach its accrual target within the next few years.

Additional funding is needed to complete the trial. Some funding has been obtained from other sources - particularly to cover the central personnel costs of the trial, and some of the European running costs. However, extra support is essential to build upon the collaboration already established. Continued funds are requested from the US Army Breast Cancer Program to help complete accrual and to ensure long-term follow-up of women randomized to ensure that the main objective of the trial is fulfilled and the scientific returns on the initial investment realized (Section D justifies this request for funding in further detail).

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APPENDIX 1

THE LANCET

Tamoxifen for early breast cancer: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group

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Articles

Tamoxifen for early breast cancer: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group**

Summary

Background There have been many randomised trials of adjuvant tamoxifen among women with early breast cancer, and an updated overview of their results is presented.

Methods In 1995, information was sought on each woman in any randomised trial that began before 1990 of adjuvant tamoxifen versus no tamoxifen before recurrence. Information was obtained and analysed centrally on each of 37 000 women in 55 such trials, comprising about 87% of the worldwide evidence. Compared with the previous such overview, this approximately doubles the amount of evidence from trials of about 5 years of tamoxifen and, taking all trials together, on events occurring more than 5 years after randomisation.

Findings Nearly 8000 of the women had a low, or zero, level of the oestrogen-receptor protein (ER) measured in their primary tumour. Among them, the overall effects of tamoxifen appeared to be small, and subsequent analyses of recurrence and total mortality are restricted to the remaining women (18 000 with ER-positive tumours, plus nearly 12 000 more with untested tumours, of which an estimated 8000 would have been ER-positive). For trials of 1 year, 2 years, and about 5 years of adjuvant tamoxifen, the proportional recurrence reductions produced among these 30 000 women during about 10 years of follow-up were 21% (SD 3), 29% (SD 2), and 47% (SD 3), respectively, with a highly significant trend towards greater effect with longer treatment (χ^2_1=52·0, 2p<0·00001). The corresponding proportional mortality reductions were 12% (SD 3), 17% (SD 3), and 26% (SD 4), respectively, and again the test for trend was significant (χ^2_1= 8·8, 2p=0·003). The absolute improvement in recurrence was greater during the first 5 years, whereas the improvement in survival grew steadily larger throughout the first 10 years. The proportional mortality reductions were similar for women with node-positive and node-negative disease, but the absolute mortality reductions were greater in node-positive women. In the trials of about 5 years of adjuvant tamoxifen the absolute improvements in 10-year survival were 10·9% (SD 2·5) for node-positive (61·4% *vs* 50·5% survival, 2p<0·00001) and 5·6% (SD 1·3) for node-negative (78·9% *vs* 73·3% survival, 2p<0·00001). These benefits appeared to be largely irrespective of age, menopausal status, daily tamoxifen dose (which was generally 20 mg), and of whether chemotherapy had been given to both groups. In terms of other outcomes among all women studied (ie, including those with "ER-poor" tumours), the proportional reductions in contralateral breast cancer were 13% (SD 13), 26% (SD 9), and 47% (SD 9) in the trials of 1, 2, or about 5 years of adjuvant tamoxifen. The incidence of endometrial cancer was approximately doubled in trials of 1 or 2 years of tamoxifen and approximately quadrupled in trials of 5 years of tamoxifen (although the number of cases was small and these ratios were not significantly different from each other). The absolute decrease in contralateral breast cancer was about twice as large as the absolute increase in the incidence of endometrial cancer. Tamoxifen had no apparent effect on the incidence of colorectal cancer or, after exclusion of deaths from breast or endometrial cancer, on any of the other main categories of cause of death (total nearly 2000 such deaths; overall relative risk 0·99 [SD 0·05]).

Interpretation For women with tumours that have been reliably shown to be ER-negative, adjuvant tamoxifen remains a matter for research. However, some years of adjuvant tamoxifen treatment substantially improves the 10-year survival of women with ER-positive tumours and of women whose tumours are of unknown ER status, with the proportional reductions in breast cancer recurrence and in mortality appearing to be largely unaffected by other patient characteristics or treatments.

Lancet 1998; **351:** 1451–67

Introduction

In women with "early" breast cancer, all detectable cancer is, by definition, restricted to the breast (and, in the case of node-positive patients, the local lymph nodes) and can be removed surgically. But undetected micrometastatic deposits of the disease may remain that, perhaps after a delay of several years, develop into a clinically detectable recurrence that eventually causes death. It has been shown previously that the use of adjuvant tamoxifen significantly improves the 10-year survival for such women,[1-3] but uncertainty has remained about who should be treated and for how long treatment should usually continue. Many randomised trials have assessed the effects of 1 or 2 years of adjuvant tamoxifen, and others have assessed the effects of about 5 years of treatment. Some more recent trials have directly compared 5 years of treatment with either shorter or longer durations, but results from these are generally not yet available (or, where available, are not yet based on sufficiently long follow-up). This overview is therefore restricted to the trials of adjuvant tamoxifen versus no adjuvant tamoxifen (control). Many of these trials

*Collaborators listed at end of paper

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allowed or encouraged the use of tamoxifen for any women in the control group who relapsed. So, although they provide a direct assessment of the effects of adjuvant tamoxifen on recurrence rates, for mortality they involve the comparison of adjuvant tamoxifen versus no tamoxifen until relapse (ie, many of these trials actually compare the effects on survival of two different ways of using tamoxifen).

Methods

Every 5 years since 1984–85, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has undertaken systematic overviews (meta-analyses) of all randomised trials of any aspect of the treatment of early (ie, apparently resectable) breast cancer.[1-5] This report is based on data collected and finalised in 1995–96. Trial identification and data-checking procedures have been described previously.[1-3] For the analyses presented here, data were sought for all randomised trials that began before 1990 and compared adjuvant tamoxifen for any duration versus no such treatment for women with early breast cancer. As in previous reports, the trials were divided into three categories on the basis of their average intended duration of adjuvant tamoxifen: about 1 year, 2 years, or more than 2 years.[3] Since the median intended duration in the latter category of trials was 5 years, these are generally described as trials of about 5 years of adjuvant tamoxifen.

Data on each individual patient

Information was sought for each woman on her age and menopausal status at randomisation, on whether or not there had been evidence of tumour spread to the axillary or other local lymph nodes (node-positive or node-negative disease, respectively), and on the results of any oestrogen-receptor (ER) or progesterone-receptor (PR) measurements on the primary tumour. Information was also sought on the date of randomisation, the allocated treatment, and the dates of first subsequent occurrence of any contralateral breast cancer, other second primary cancer, local recurrence, distant recurrence, and death, ideally with follow-up to 1995. The cause of death was requested only for women who died without any record of distant recurrence. The data were checked for internal consistency, and were amended or updated as necessary through correspondence with the responsible trialists. Before being finalised, the overview analyses were presented and discussed at a meeting in September, 1995, of the investigators who had conducted the trials. In addition, this report was circulated to them and to other members of the EBCTCG, and revised in the light of their comments.

In this report, women classified as node-positive include about 85% reported to have surgically confirmed nodal involvement, plus 10% with nodal status unreported (who had about the same prognosis as those with confirmed involvement), 5% reported by unspecified criteria to have nodal involvement, and less than 1% reported to have had only clinical evidence of involvement. Those classified as node-negative include about 80% reported to have no nodal involvement after axillary clearance, plus 12% with negative axillary sampling, 7% reported by unspecified criteria to be without nodal involvement, and 2% reported to have had only clinical evidence of lack of involvement. Three categories of ER status at entry are defined.[3] ER-positive was defined as at least 10 fmol ER per mg cytosol protein where quantitative measurements were available, but was otherwise accepted as reported. All other women whose ER status was supplied were defined as ER-poor, leaving a third group (ER unknown) in whom ER status was unreported. For PR status, the same three definitions were used. In general, women with unrecorded ER status also have unrecorded PR status, but the converse is not necessarily true. For certain analyses, ER-positive tumours were further subdivided into ER++ (ie, at least 100 fmol per mg) and ER+ (10–99 fmol per mg or no quantitative measure available).

Mean scheduled duration of adjuvant tamoxifen treatment	Available		Not available	
	Number of trials*	Number of women	Number of trials	Number of women
≤1 year	14	9128	1	100 (1%)
2 years	32	19 212†	4	1400 (7%)
≥3 (median 5) years	9	8349	3‡	4200 (33%)
Any duration	55	36 689†	8	5700 (13%)

*ACETBC-1 study is counted as two trials, as is the Stockholm B study.
†Amsterdam C8209 trial randomised women evenly between 1 year, 3 years, and control; to achieve balanced numbers, some totals elsewhere count these 410 control patients twice.
‡Three large unpublished trials that began shortly before 1990.

Table 1: **Availability of data from randomised trials that began before 1990 of adjuvant tamoxifen versus no adjuvant tamoxifen**

Statistical methods

The statistical methods have been described in detail elsewhere,[1-3] with comparisons based on the intention-to-treat principle. First each trial was analysed separately, and then the resulting log-rank statistics, one per trial, were combined to give an overall estimate of the effect of tamoxifen. When information from different trials is combined in this way, women in one trial are compared directly only with other women in the same trial, and not with women in another trial. The combination of evidence from different trials yields, as an overall estimate of the effect of treatment in those trials, a weighted average of the apparent effect of treatment in each separate trial: it does not, however, implicitly assume that the true effect of treatment is the same in each trial.

The principal events analysed were recurrence and death. Recurrence was defined as the first reappearance of breast cancer at any site (local, contralateral, or distant), as in previous overview analyses.[1-3] Deaths from unknown causes were included with deaths from breast cancer, unless the trialist specifically stated that breast cancer was not the cause. The few women who were recorded as having died of breast cancer, or from an unknown cause, without any record of any recurrence (9% of "breast cancer" deaths) were analysed as though they had had a recurrence just before they died. Women who were recorded as having died from other causes without a recorded recurrence were censored at the date of death in the analyses of recurrence as first event, and vice versa. Analyses of breast cancer deaths involve log-rank subtraction to avoid bias[4,5] (ie, the log-rank statistics for death before recurrence are subtracted from those for overall survival). Tests for trend relate median intended years of tamoxifen (1, 2, or 5) in the three categories of trial to the log-rank observed minus expected (O−E) values. If w is the weighted average of these durations, with weights proportional to the log-rank variances, we test whether $(w-1)(O_1-E_1) + (w-2)(O_2-E_2) + (w-5)(O_5-E_5)$ is non zero.

Two-sided significance tests are used (hence $\chi^2_1=3{\cdot}84$ is described not as $p=0{\cdot}05$ but as $2p=0{\cdot}05$), except for χ^2 tests on more than one degree of freedom. Standard deviation (SD) is interchangeable with standard error (hence 25 [SD 2] denotes 25 with standard error 2). Exact values are usually given for $2p<0{\cdot}1$ and NS (not significant) is sometimes used to denote $2p>0{\cdot}1$ even though some results with $2p<0{\cdot}1$ could also arise by chance.

Proportional benefits and absolute benefits

Throughout this report, the effects of treatment are described either as proportional benefits (eg, as a 25% reduction in the death rate) or as absolute benefits. (Terminology: a proportional reduction of a quarter in the annual odds of death might equivalently be described as an odds ratio of 0·75, a hazard ratio of 0·75, an odds reduction of 25%, or a 25% reduction in the death rate. Similarly, in the tables, a ratio of rates of 0·75 corresponds to a 25% reduction in the rate.) For a given proportional reduction in the death rate, the absolute improvement in 10-year survival is bigger for women with node-positive than for those with node-negative disease. Roughly, in

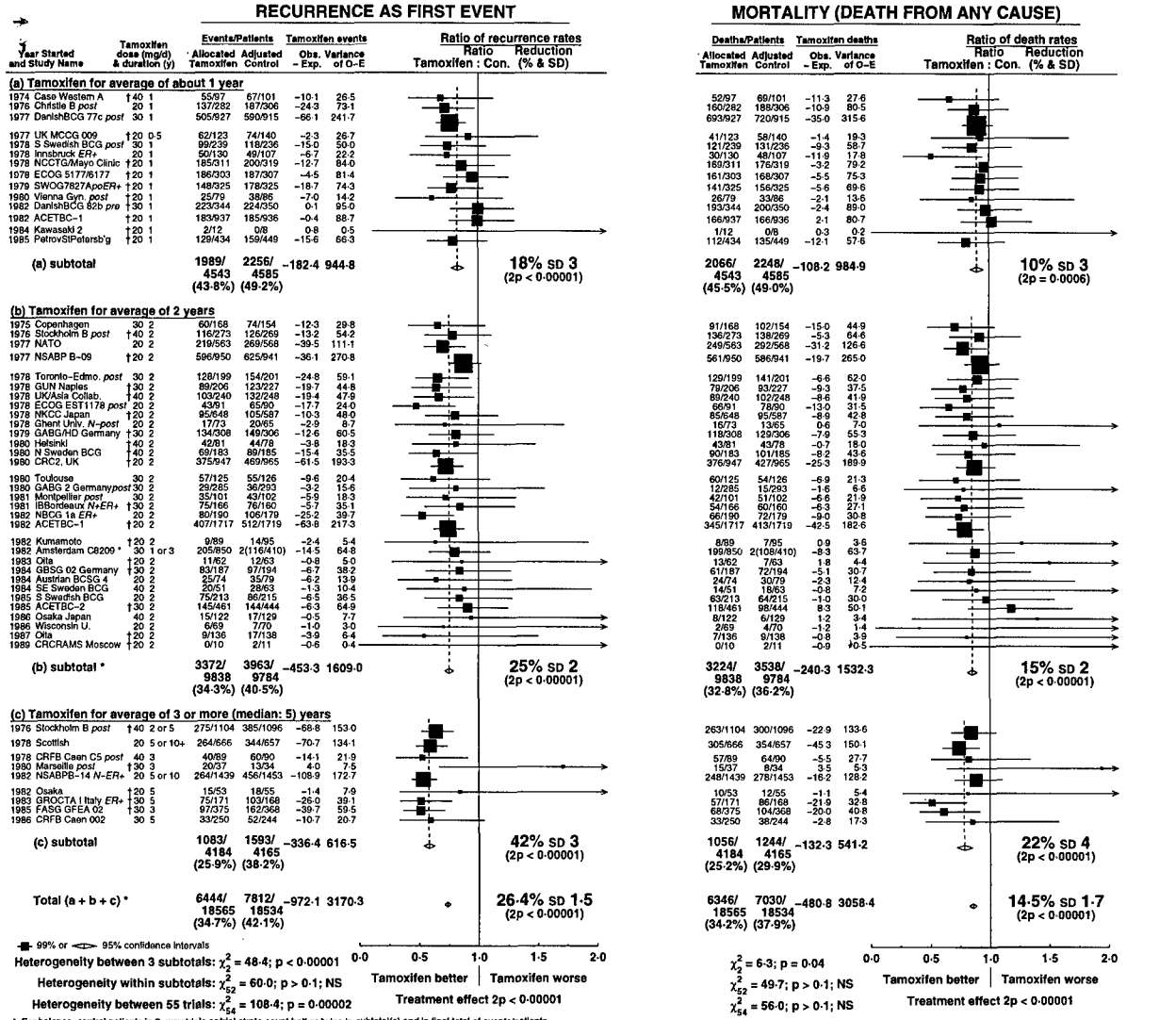

Figure 1: **Separate results from all 55 tamoxifen trials, subdivided by scheduled duration of adjuvant tamoxifen**

A: recurrence as a first event (including contralateral breast cancer, and censoring at the time of death from another cause without any recurrence). B: all-cause mortality.

Each trial is described by one line of data, giving the year that randomisation began, an abbreviated trial name, and the adjuvant tamoxifen schedule (mg/day and duration in years; †indicates randomisation of tamoxifen plus chemotherapy versus the same chemotherapy alone), followed by the recurrence and mortality analyses. The area of each black square is proportional to the amount of information contributed by the trial it describes, so larger squares are associated with shorter CIs (ie, with more informative results). The solid vertical line indicates a ratio of 1·0 (ie, no difference between treatment and control), and results to the left of it favour tamoxifen. For each category of trials from which the results are combined, the overall ratio and its 95% CI are shown by a broken vertical line together with a small diamond-shaped symbol, next to which is the corresponding proportional reduction (% and SD). Subtotals for the trials of 1, 2, and about 5 years of tamoxifen are provided, as are the χ^2 tests for heterogeneity between these subtotals. Tests for trend with respect to the median tamoxifen duration (1, 2, or 5 years) yield χ^2_1=48·4 for recurrence (2p<0·00001) and χ^2_1= 6·2 for mortality (2p=0·013). *For balance, the 410 control patients in the only three-way trial count twice in the adjusted control totals, but all other statistical analyses involve unadjusted numbers. The remaining trials were approximately evenly randomised.

these particular trials, the ratio of the absolute to the proportional mortality reduction during the first 10 years will be about two-fifths for node-positive patients and one-fifth for node-negative patients. Thus, for example, a 25% reduction in the death rate might produce an absolute benefit of about 10% for patients with node-positive disease (eg, improving the 10-year survival from 50% to about 60%), but only about a 5% absolute benefit for those with node-negative disease (eg, improving the 10-year survival from 75% to about 80%).

Numbers available

63 randomised controlled trials of adjuvant tamoxifen versus no adjuvant tamoxifen that began before 1990 were identified, involving a total of more than 42 000 women (table 1). This total is substantially more than in the previous cycle of this collaboration,[3] because some trials were then still recruiting, some were unavailable, and those that began in 1985–89 were not eligible. Of the 63 trials, some scheduled no adjuvant chemotherapy for either group, but others randomised tamoxifen plus chemotherapy versus the same chemotherapy alone. 55 of the 63 trials were available for these analyses, and eight were not. Three of the unavailable trials are large unpublished trials (CRC under 50s, SWOG 8897, and ECOG 5188) that began shortly before 1990 and have as yet made no results available. Although these three trials involve a total of more than 5000 women, they would by 1995 have collected information on only a limited number of deaths, most of which would have occurred during the first few years after randomisation (when there is already much evidence from other trials about the effects of tamoxifen). Information from the trials of 1 or 2 years of tamoxifen is 95% complete. Overall, therefore, the amount of missing data is probably too small to affect the overall analyses presented here in

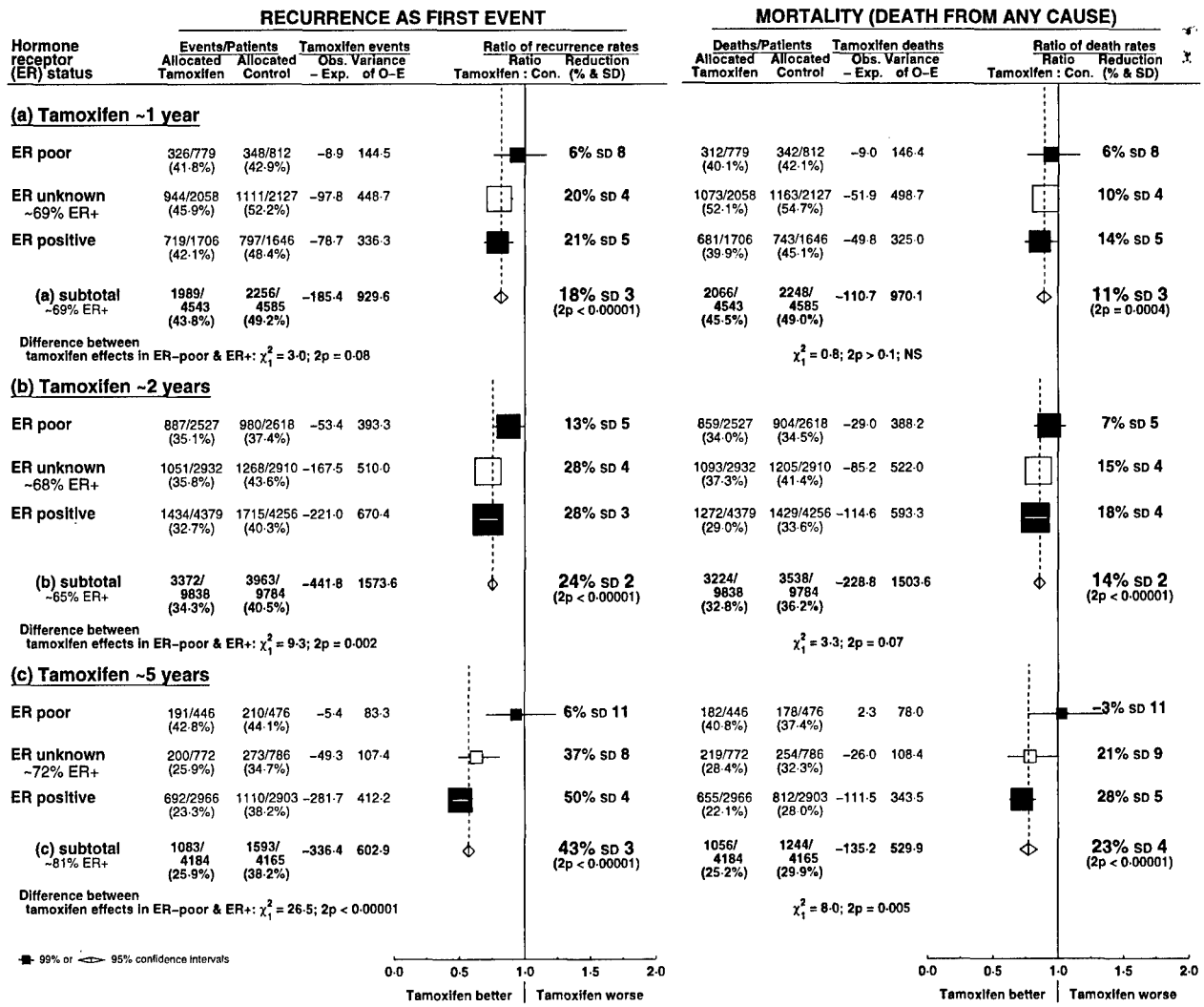

Figure 2: **Proportional risk reductions, subdivided by tamoxifen duration and by ER status**

Each line describes a subtotal, combining the results from particular types of women in particular categories of trial. Here and in figures 3–7, when some women have tumours of unknown ER status an estimate is given of the proportion who, if they had been tested, would have had ER-positive tumours (estimated as half the women aged under 50, and three-quarters of the others[7]). The black squares relate to the effects of treatment among women whose primary tumour was of known ER status (ie, ER-positive or ER-poor), and the white squares relate to those among women whose tumours were of unknown ER status. For the 18 000 women with ER-positive disease, the trend test for increasing benefit with increasing tamoxifen duration yields χ^2_1=45·5 (2p<0·00001) for recurrence and χ^2_1=5·6 (2p=0·018) for mortality. For the 8000 women with ER-poor disease, the trend test yields χ^2_1=0·02 (NS) for recurrence and χ^2_1=0·53 (NS) for mortality.

any important way (although the three large trials should contribute substantially to the reliability of certain subgroup results in future cycles of the overview).

Data on each individual patient were provided for 36 689 women in the 55 trials available, with 14 140 first recurrences and 13 268 deaths during an average of about 10 years of follow-up. 88% (32 422) of the women were in trials that reported contralateral breast cancer separately, and in these trials 8% (839) of the first recurrences involved a new primary cancer in the opposite breast. 90% (32 947) of the women were in trials that distinguished between deaths from breast cancer and from other causes, and in these trials 14% of the deaths were specified as being due to causes other than breast cancer and were not preceded by any record of breast cancer recurrence. Only these deaths are defined in the present analyses as being non-breast-cancer deaths.

In the previous cycle of this overview, the analyses of adjuvant tamoxifen versus no adjuvant tamoxifen involved 11 095 first recurrences and 8219 deaths among 29 892 women.[3] The main increases since then are in the amount of evidence from trials of about 5 years of tamoxifen, which has increased from 1038 deaths among 6398 women[3] to 2300 among 8349, and in the amount of evidence on events occurring more than 5 years after randomisation. The extra data increase the statistical stability of the estimated effects in trials of about 5 years of tamoxifen, in later time periods, and in particular subgroups of women.

Results

The general structure of each figure is similar: the left-hand side describes recurrence rates and the right-hand side describes mortality rates, while the upper, middle, and lower parts describe the trials of 1 year, 2 years, and about 5 years of adjuvant tamoxifen, respectively. Figures 1 and 2 include all women with relevant data (as do the tables). Figures 3–7 exclude women recorded as having had ER-poor tumours.

Overall findings

Figure 1 shows the results from each of the 55 trials, irrespective of duration of follow-up, with subtotals for the trials of 1 year, 2 years, and about 5 years of adjuvant tamoxifen. The totals at the bottom of figure 1 show that, both for recurrence as a first event and for mortality, allocation to tamoxifen produces highly statistically

significant ($2p<0{\cdot}00001$) benefits after a median of about 10 years of follow-up. However, comparisons of the subtotals suggest that the proportional risk reductions may depend on the scheduled duration of tamoxifen.

For recurrence, the proportional reductions in the trials of 1 year, 2 years, and about 5 years of tamoxifen were 18% (SD 3), 25% (SD 2), and 42% (SD 3), which are all highly significantly different from zero (each $2p<0{\cdot}00001$). The heterogeneity between these three recurrence reductions is highly significant ($\chi^2_2=48{\cdot}4$, $p<0{\cdot}00001$), as is the test for trend with respect to tamoxifen duration ($\chi^2_1=48{\cdot}4$; $2p<0{\cdot}00001$). By contrast, when trials of similar tamoxifen durations are compared with each other, no significant heterogeneity remains between the recurrence reductions ($\chi^2_{52}=60{\cdot}0$, NS).

For mortality, the proportional reductions in the death rates in the trials of 1 year, 2 years, and about 5 years of tamoxifen were 10% (SD 3), 15% (SD 2), and 22% (SD 4), which are all highly significantly different from zero (two with $2p<0{\cdot}00001$). Although the heterogeneity between these three mortality reductions is only marginally significant ($\chi^2_2=6{\cdot}3$, $p=0{\cdot}04$), the test for trend provides somewhat clearer evidence of there being a greater mortality reduction in the trials of longer adjuvant treatment ($\chi^2_1=6{\cdot}2$, $2p=0{\cdot}013$). Again, when trials of similar tamoxifen durations are compared with each other, no significant heterogeneity remains between the mortality reductions ($\chi^2_{52}=49{\cdot}7$, NS).

These comparisons of different durations of tamoxifen involve indirect comparisons between the effects of treatment in the subtotals for the randomised trials of different durations of adjuvant tamoxifen versus no adjuvant tamoxifen, rather than direct randomised comparisons of different durations of tamoxifen. Hence, the apparent differences in the effects observed in these indirect comparisons may be due, at least partly, to systematic differences in the types of patient studied or in the trial design. For example, in the trials of shorter tamoxifen durations, a smaller proportion of the women had ER-positive tumours and the duration of follow-up was longer.

Hormone receptors

Figure 2 subdivides the overall results by what is known about the ER status of the primary cancer. For each tamoxifen duration, the proportional reduction in recurrence appears to be greater for patients with ER-positive tumours than for patients with ER-poor tumours, and this heterogeneity in therapeutic effect is most definite in the trials of about 5 years of tamoxifen (χ^2_1 for heterogeneity=26·5, $2p<0{\cdot}00001$). Likewise, for each tamoxifen duration, the proportional reduction in mortality appears to be greater for patients with ER-positive tumours than for patients with ER-poor tumours, and again this heterogeneity in therapeutic effect is most definite in the trials of about 5 years of tamoxifen (χ^2_1 for heterogeneity=8·0, $2p=0{\cdot}005$).

Women with ER-positive tumours—Among the 18 000 women with ER-positive tumours (figure 2), the proportional reductions in the recurrence rates in the trials of 1 year, 2 years, and about 5 years of tamoxifen were 21% (SD 5), 28% (SD 3), and 50% (SD 4). These recurrence reductions are all highly significant (each $2p<0{\cdot}00001$), as is the trend between them ($\chi^2_1=45{\cdot}5$, $2p<0{\cdot}00001$). Separate consideration of women with ER+ and ER++ tumours indicated greater proportional reductions in recurrence among the latter (ie, among women with at least 100 fmol receptor per mg cytosol protein). For example, in the trials of about 5 years of tamoxifen, the reductions were 43% (SD 5) and 60% (SD 6), respectively, for women with ER+ and ER++ tumours. The proportional mortality reductions among women with ER-positive tumours were 14% (SD 5), 18% (SD 4), and 28% (SD 5) in the trials of 1, 2, and about 5 years of tamoxifen. Each of these three mortality reductions is also significant, as is the trend between them ($\chi^2_1=5{\cdot}6$, $2p=0{\cdot}018$). Again, the effects appeared to be greater in women with ER++ tumours: in the trials of about 5 years of tamoxifen, the reductions in mortality were 23% (SD 6) and 36% (SD 7) for women with ER+ and ER++ tumours.

PR measurements may be predictive of treatment response in advanced disease.[6] But, in this analysis of early breast cancer among women with ER-positive tumours, the available PR measurements were of little additional value in predicting the response to tamoxifen. Thus, among the 2000 women with ER-positive, PR-poor tumours, the recurrence reduction produced by tamoxifen was 32% (SD 6; $2p<0{\cdot}00001$) and the mortality reduction was 18% (SD 7; $2p=0{\cdot}01$), which are not materially different from the corresponding reductions of 37% (SD 3; $2p<0{\cdot}00001$) and 16% (SD 4; $2p<0{\cdot}00001$) among the 7000 women with ER-positive, PR-positive tumours. If attention is restricted to the trials of about 5 years of tamoxifen, there is again good evidence of benefit in the women with ER-positive, PR-poor tumours (recurrence reduction 46% [SD 9; $2p<0{\cdot}00001$], mortality reduction 28% [SD 11; $2p=0{\cdot}01$]).

Women with ER-poor tumours—Among the 8000 women with ER-poor tumours (figure 2), the benefits of treatment were less clear. Overall, irrespective of the duration of tamoxifen that was tested, the proportional recurrence reduction was 10% (SD 4; $2p=0{\cdot}007$; 95% CI 2–17%). Although this result is statistically significant, the apparent benefit is small, and the lower confidence limit is close to zero. If contralateral breast cancers (the receptor status of which may be largely unrelated to that of the original primary) were not included, the overall proportional recurrence reduction would be 9% (SD 4; $2p=0{\cdot}02$; 95% CI 1–16%). The proportional recurrence reductions in the trials of 1 year, 2 years, and about 5 years of tamoxifen were 6% (SD 8; NS), 13% (SD 5; $2p=0{\cdot}01$), and 6% (SD 11; NS), respectively, with no evidence of any trend towards greater benefit with longer tamoxifen treatment ($\chi^2_1=0{\cdot}02$, NS).

The mortality results among the women with ER-poor tumours appeared even less promising than those for recurrence. Overall, irrespective of tamoxifen duration, the mortality reduction was only 6% (SD 4; NS). In the trials of 1, 2, and about 5 years of tamoxifen, the mortality reductions were 6% (SD 8; NS), 7% (SD 5; NS), and −3% (SD 11; NS); again, there is no suggestion of any trend towards greater benefit with longer treatment ($\chi^2_1=0{\cdot}53$, NS).

It is difficult to know whether these recurrence and mortality results represent real benefit in some women whose tumours would, even by the best current ER assay methods, still be wholly ER-negative, or whether they reflect real benefit only among women whose tumours

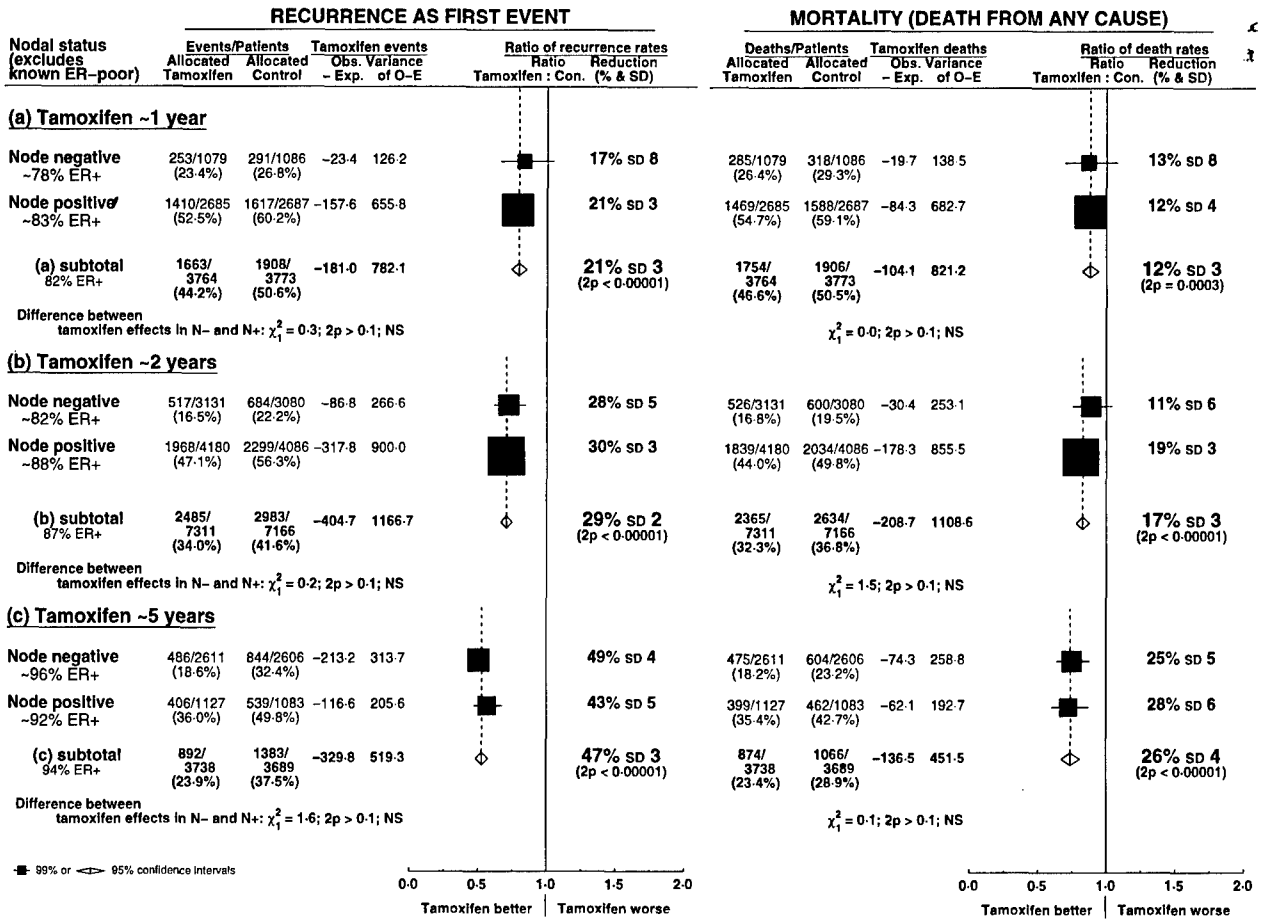

Figure 3: **Proportional risk reductions, subdivided by tamoxifen duration and by nodal status (after exclusion of women with ER-poor disease)**

Although women with ER-poor disease have been excluded, the ER status was unreported for more than a third of those that remain, and an estimate of the overall proportion who would, if tested, have had ER-positive disease is given for each line of analyses. Overall, the estimated proportions with ER-positive disease are about 82%, 87%, and 94%, respectively, in the trials of 1, 2, or about 5 years of tamoxifen. The tests for trend between the effects of 1, 2, and about 5 years of tamoxifen in these predominantly ER-positive women yield χ^2_1=52·0 (2p<0·00001) for recurrence and χ^2_1=8·8 (2p=0·003) for mortality.

would have had detectable, albeit low, receptor levels by current methods.[6] In women with ER-poor tumours, there was not enough evidence to determine whether PR measurements could help predict the response to tamoxifen. Among the 2000 women with ER-poor, PR-poor tumours, tamoxifen had no apparent effect on recurrence or mortality rates (1% [SD 7] reduction in both cases), whereas among the 602 women with ER-poor, PR-positive tumours, the recurrence reduction was 23% (SD 12; 2p=0·05) and the mortality reduction was 9% (SD 14; NS). The numbers of women in these subgroups are, however, not large, so the analyses are unstable. Hence, the existence of some real benefit cannot be excluded for those women whose tumours were ER-poor, PR-poor, and cannot be assumed for those whose tumours were ER-poor, PR-positive.

Women with unrecorded ER status—About half of the tumours in women aged under 50 and about three-quarters of those in women aged over 50 would have been classified as ER-positive by the assays available some years ago.[7] Hence, it can be estimated that about two-thirds of the women whose tumours were of unrecorded ER status in these trials would, if measured, have had ER-positive tumours. If so, the observed effects of tamoxifen among the women with tumours of unrecorded ER status should be at least two-thirds of the effects observed in those recorded as having ER-positive tumours. The highly significant benefits among the 12 000 women with tumours of unrecorded ER status in figure 2 support this estimate. 99% of the tumours with unrecorded ER status also had unrecorded PR status.

Effects on recurrence and mortality after exclusion of women with ER-poor tumours

Even though there may be some benefit among some of the women classified as having ER-poor tumours, the subsequent analyses of recurrence or of total mortality include only the 18 000 women with confirmed ER-positive tumours and the 12 000 women with tumours of unrecorded ER status (of which about 8000 would be expected to have been ER-positive), among whom there is clear evidence of substantial benefit. Figure 2 shows that further restriction to just those with tumours that were known to be ER-positive would not have materially affected the apparent sizes of the effects of treatment on recurrence or on mortality.

Because figures 3–7 exclude women with ER-poor tumours, the proportion with ER-positive tumours is larger and the risk reductions are slightly more extreme than those in figure 1, as are the trends towards greater benefit with longer tamoxifen duration (trend tests in figure 3: for recurrence, χ^2_1=52·0, 2p<0·00001; for

mortality, χ^2_1=8·8, 2p=0·003). The estimated proportions with ER-positive tumours still differ slightly between the trials of 1 year, 2 years, and about 5 years of tamoxifen (82%, 87%, and 94%, respectively), but these differences can account for only a small part of the trend in efficacy.

Nodal status—Both for recurrence and for mortality, the proportional risk reductions within each category of tamoxifen duration appear to be about the same for women with node-positive disease as for women with node-negative disease (figure 3). All six of the χ^2 tests for heterogeneity between the proportional risk reductions produced by tamoxifen in women with node-positive and those with node-negative disease are non-significant. At least in terms of 10-year outcome, the same proportional benefit for node-positive as for node-negative disease would generally imply a greater absolute benefit for women with node-positive disease. These absolute benefits are illustrated in figure 4 for the effects of 1, 2, and about 5 years of adjuvant tamoxifen.

The left side of figure 4 describes the proportions who would, in the absence of other causes of death, still be alive and free of any recurrence of breast cancer. For the trials of 1 or 2 years of tamoxifen, the absolute improvements in this 10-year recurrence risk appear larger for women with node-positive disease than for those with node-negative disease. In the trials of about 5 years of tamoxifen, the absolute improvement in this 10-year recurrence risk appears to be about as great for women with node-negative disease (absolute improvement 14·9% [SD 1·4]) as for those with node-positive disease (absolute improvement 15·2% [SD 2·5]). This finding could well be because the play of chance has led to slight overestimation of the effects of 5 years of tamoxifen in women with node-negative disease (for example, through a higher recurrence rate in the control group than in the other trials) or to slight underestimation of the effects in women with node-positive disease. Still, however, the real benefits from 5 years of tamoxifen must be substantial for both types of patient.

The right side of figure 4 describes all-cause mortality. The absolute improvements in 10-year survival appear greater for women with node-positive disease than for those with node-negative disease in each category of tamoxifen duration. For patients with node-negative disease in the trials of 1, 2, and about 5 years of tamoxifen the absolute improvements in 10-year survival are 3·4% (SD 2·1; 2p=0·09), 2·3% (SD 1·3; 2p=0·06), and 5·6% (SD 1·3; 2p<0·00001) respectively, whereas for those with node-positive disease the absolute improvements are 4·5% (SD 1·4; 2p=0·001), 7·2% (SD 1·2; 2p<0·00001), and 10·9% (SD 2·5; 2p<0·00001). The mortality in figure 4 is not all due to breast cancer: indeed, analyses of the deaths before recurrence indicate that even in the absence of breast cancer, only about 92% of these women would have survived 10 years from randomisation. Since tamoxifen has little effect on the aggregate of all other causes of death (see below), restriction to breast cancer deaths would make little difference to the estimated absolute benefits, but would slightly increase the proportional mortality reductions, especially for women with node-negative disease (data not shown).

Benefits during the first 5 years and later—The main divergence between the recurrence graphs for tamoxifen and control takes place during the first 5 years, with a substantial benefit already apparent during the first year after randomisation (left side of figure 4). For mortality, however (right side of figure 4), there was no apparent benefit during the first year after randomisation, but there was benefit during the next 4 years. Thus, 5 years after randomisation there was a significant difference in survival, and during the next 5 years this grew significantly larger. Figure 5 provides separate analyses of the effects of treatment on the proportional risk reductions during years 0–4 and later (years 5+).

For recurrence (left side of figure 5), the proportional reductions during years 0–4 were 22% (SD 4), 34% (SD 3), and 51% (SD 4) in the trials of 1, 2, and about 5 years of tamoxifen (each 2p<0·00001), with a significant trend (χ^2_1=51·3, 2p<0·00001) towards greater effect with longer treatment. Among women still free of recurrence 5 years after randomisation, those who had originally been allocated tamoxifen still had a somewhat better prognosis than those who had not: the proportional reductions in the rate of recurrence in years 5 and later were 14% (SD 7), 5% (SD 6), and 33% (SD 7), respectively. Again there is a significant trend towards a greater effect with longer treatment (χ^2_1=7·2; 2p=0·007) but, considered separately, only the additional benefit with about 5 years of tamoxifen was clearly significantly different from zero (2p<0·00001). Thus, in the trials of about 5 years of adjuvant tamoxifen, the recurrence rate was reduced by about half during years 0–4 and by about one-third during the next few years. This additional benefit occurred despite the fact that by the end of the first 5 years the tamoxifen group included substantial numbers of women who would, in the absence of tamoxifen, already have relapsed, whereas the control group did not. Of the recurrences after the first 5 years in tamoxifen-allocated women, one-third involved women who had been re-randomised to continue tamoxifen during years 5–9, but two-thirds involved women who had been allocated to stop taking tamoxifen by the end of year 4. If most of them did stop, part of the reduction in the recurrence rate after the first 5 years would represent a carry-over effect, whereby adjuvant tamoxifen reduces the recurrence rate not only while treatment continues but also for some years afterwards.

For mortality (right side of figure 5), an unexpected[3] feature of these results is that the proportional risk reductions during the period after the first 5 years were remarkably similar to those during years 0–4. The proportional mortality reductions during years 0–4 were 11% (SD 4; 2p=0·02), 17% (SD 4; 2p<0·00001), and 28% (SD 6; 2p<0·00001) in the trials of 1, 2, or about 5 years of tamoxifen. The corresponding proportional mortality reductions during years 5 and later were similar, being 13% (SD 5; 2p=0·009), 15% (SD 4; 2p=0·0003), and 24% (SD 6; 2p=0·00005), respectively. Hence, a few years of tamoxifen significantly improves the proportion surviving for 5 years and, in addition, having previously had such treatment significantly improves the subsequent prognosis of women who have already survived 5 years.

Different treatment regimens—The daily dose of tamoxifen was 20 mg in about half the trials and 30–40 mg in the other trials. In terms both of recurrence and of mortality, the benefits appeared to be about as big in the trials of 20 mg/day as in the trials of 30–40 mg/day

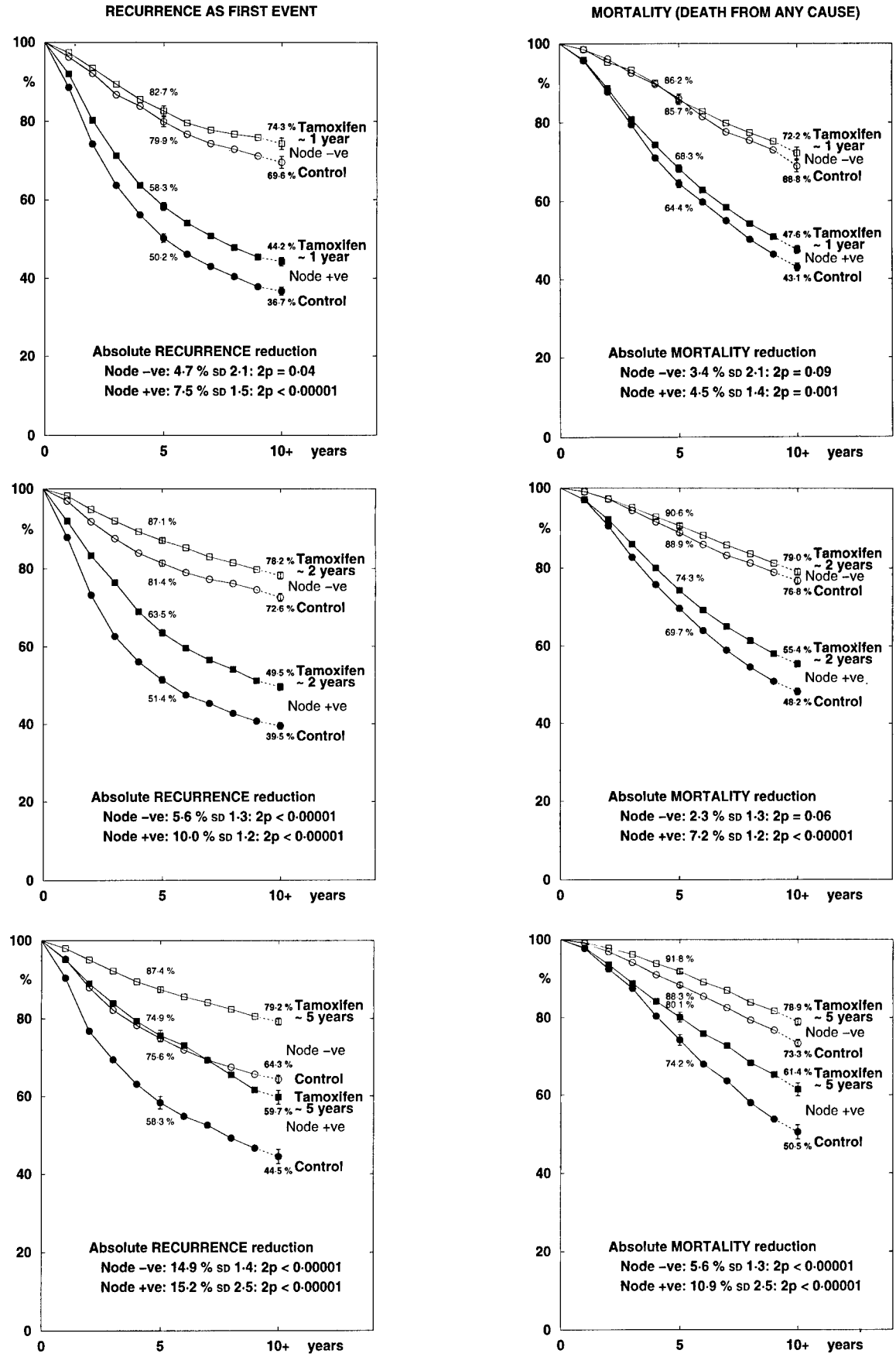

Figure 4: **Absolute risk reductions during the first 10 years, subdivided by tamoxifen duration and by nodal status (after exclusion of women with ER-poor disease)**

In these generalised Kaplan-Meier curves, the values for the tamoxifen and control patients at 5 years and at 10 years are given beside each pair of lines. Differences in 10-year outcome, together with their standard errors, are given below the lines.

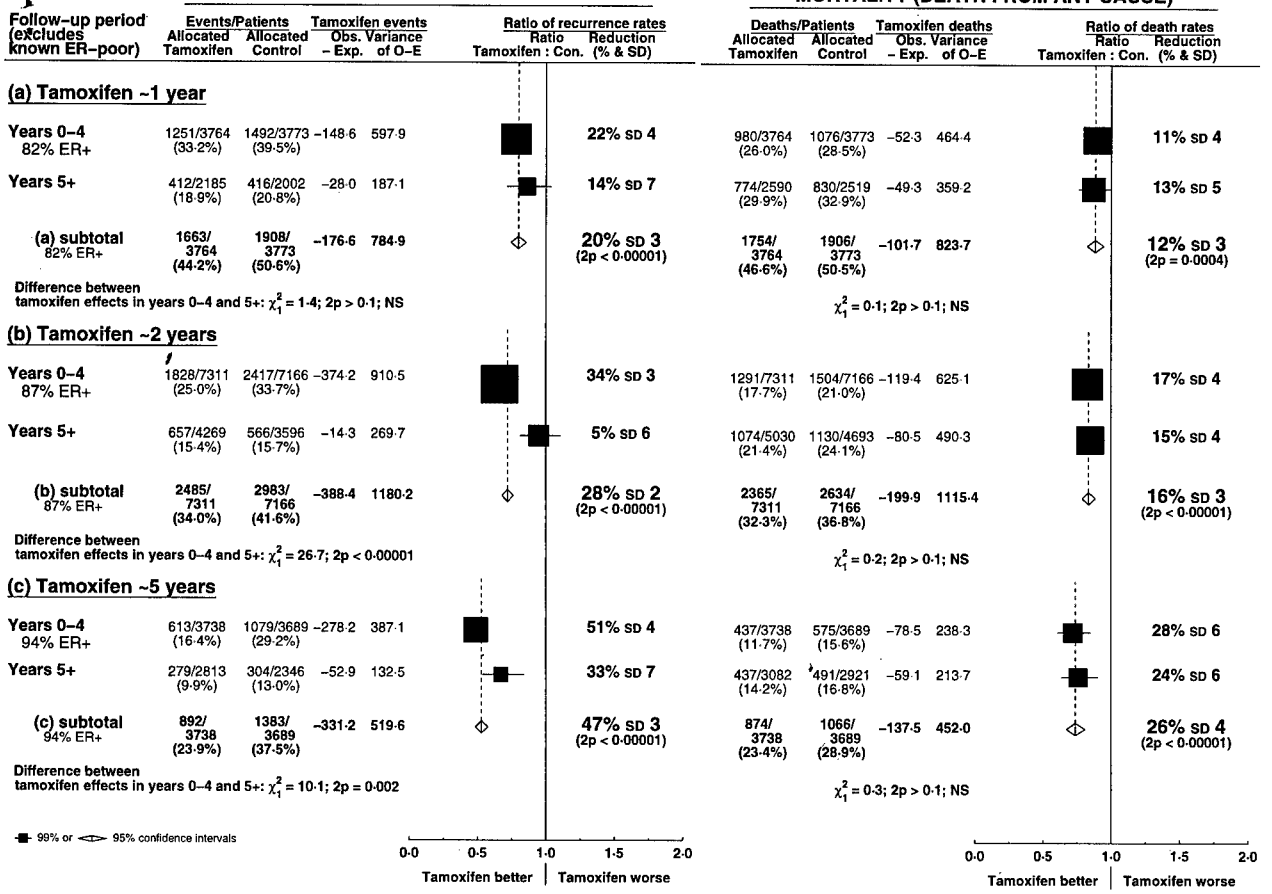

Figure 5: **Proportional risk reductions during the first 5 years (0–4) and later, subdivided by tamoxifen duration (after exclusion of women with ER-poor disease)**

(figure 6). No major trial, however, has involved a directly randomised comparison between different daily doses of tamoxifen.

Some of the trials were of adjuvant tamoxifen versus no systemic adjuvant therapy, with no adjuvant chemotherapy scheduled for either group (Tam *vs* nil in figure 6), whereas others were of adjuvant tamoxifen plus chemotherapy versus the same chemotherapy alone (Tam + C *vs* C in figure 6). For recurrence (left side of figure 6), the proportional reductions in the trials of 1 or 2 years of tamoxifen were significantly larger in the absence of chemotherapy than in its presence. But in the trials of about 5 years of adjuvant tamoxifen the recurrence reductions seemed equally large in the absence and the presence of chemotherapy. In each case, however, irrespective of whether chemotherapy was to be used, tamoxifen was of benefit in delaying recurrence. The same appears to be true for mortality (right side of figure 6): indeed, perhaps chiefly by chance, the mortality reduction appears to be particularly great in the trials of about 5 years of tamoxifen plus chemotherapy versus the same chemotherapy alone.

Age and menopausal status—In the trials of 1 or 2 years of tamoxifen there are significant trends towards greater recurrence reductions in older than in younger women (left side of figure 7). But in the trials of about 5 years of tamoxifen this trend is weaker, and there was a 45% (SD 8) reduction among those aged under 50 when randomised (about 92% of whom had ER-positive disease). This benefit is so much greater than that among the younger women in trials of shorter tamoxifen durations (about three-quarters of whom also had ER-positive tumours) that some of it may be due to chance. But the 99% CI is narrow, and the recurrence reductions produced by about 5 years of tamoxifen are substantial and highly significant both in the women aged under 40 when randomised (54% [SD 13] reduction) and in those aged 40–49 (41% [SD 10] reduction). Hence, much of the apparent benefit of about 5 years of tamoxifen in young women with ER-positive tumours must be real.

For mortality (right side of figure 7) the patterns are similar, but less stable. In the trials of 1 or 2 years of tamoxifen there are slight trends towards greater mortality reductions at older ages, but these trends are not clearly significant, and no such trend is apparent in the trials of about 5 years of tamoxifen. Among women who were older than 70 when randomised, many of the deaths during the next 10 years will have been from causes unrelated to the original breast cancer, and this factor may have diluted any trends in the effects of treatment on all-cause mortality.

Women aged 40–49 and those aged 50–59 were further subdivided by their menopausal status when randomised. In neither case, however, did this subdivision significantly affect the age-specific results (data not shown).

Finer subdivision of the evidence—After the effects of tamoxifen have been subdivided by treatment duration, further subdivision by just one other factor (as in the various figures) may be somewhat unreliable and further subdivision by two other factors may be very unreliable.

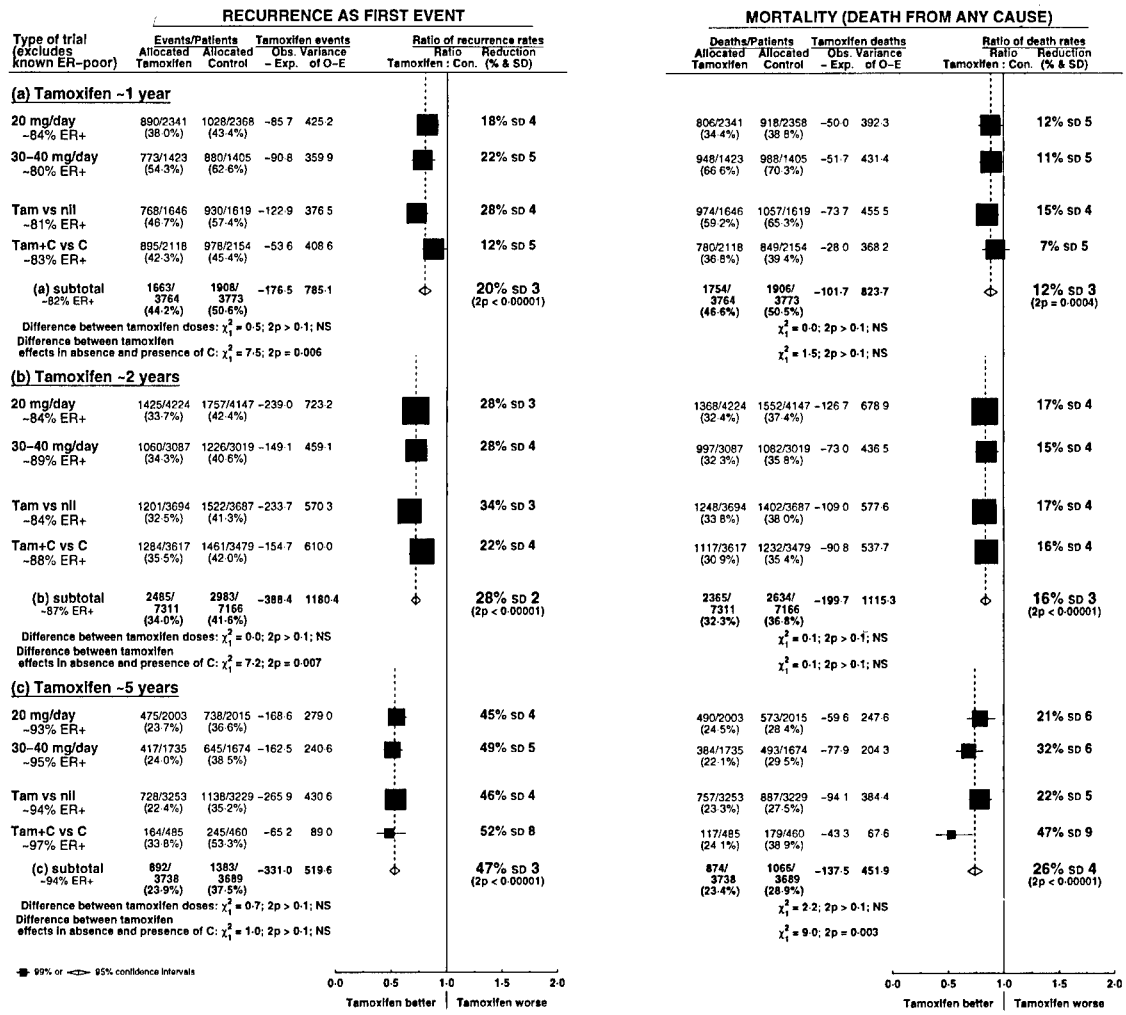

Figure 6: **Proportional risk reductions, subdivided by tamoxifen duration and either by daily tamoxifen dose or by whether women were all to avoid chemotherapy or all to receive it (after exclusion of women with ER-poor disease)**
Tam vs nil denotes trials in which neither group was scheduled to receive adjuvant chemotherapy; Tam+C vs C denotes trials of tamoxifen plus adjuvant chemotherapy versus the same chemotherapy alone.

For example, the reductions in recurrence in the trials of about 5 years of tamoxifen were highly significant, and appeared to be of similar magnitude, in the women aged under 50 when randomised and in those aged 50 or over (figure 7). Similarly, the reductions in recurrence with about 5 years of tamoxifen appeared to be about the same, and again highly significant, in the absence of adjuvant chemotherapy and in its presence (figure 6). However, although the effects of 5 years of tamoxifen on recurrence were significant and appeared to be similar after subdivision of the available data with respect to both age and concurrent chemotherapy (age less than 50, 47% [SD 8] recurrence reduction in the absence and 40% [SD 19] in the presence of chemotherapy; age more than 50, 45% [SD 4] recurrence reduction in the absence and 54% [SD 8] in the presence of chemotherapy), this is not statistically reliable evidence that the real sizes of these four effects are similar. The same is true of the apparent similarity of the effects of 5 years of tamoxifen on mortality in these same subdivisions (age less than 50, 30% [SD 12] and 39% [SD 22] mortality reductions; age more than 50, 20% [SD 5] and 49% [SD 10] mortality reductions). Even such a large data-set cannot reliably support such excessively fine subdivision of the available evidence.

Effects of tamoxifen on other outcomes

Table 2 describes the effects of tamoxifen on various other outcomes: incidence of contralateral breast cancer (which has also been included in all previous analyses of recurrences, accounting for 8% of them), incidence of colorectal and endometrial cancer (including both fatal and non-fatal cases, as long as there had been no previous recurrence of breast cancer), and death from endometrial cancer or from a cause other than breast or endometrial cancer (among women with no previous recurrence of breast cancer recorded). Since the hormone-receptor status of the original breast cancer may have little relevance to the effects of tamoxifen on these other outcomes, women with ER-poor disease are not excluded from these analyses (although their exclusion would not materially alter the findings in table 2). Most trials provided data on all of these other outcomes, but a few reported on only some of them, introducing slight differences between the denominators in different parts of table 2.

For these analyses of other outcomes, the period at risk involves only the time before any breast cancer recurrence, which, since adjuvant tamoxifen delays recurrence, is an average of about 10% longer for those allocated tamoxifen than for those not (6% longer in the

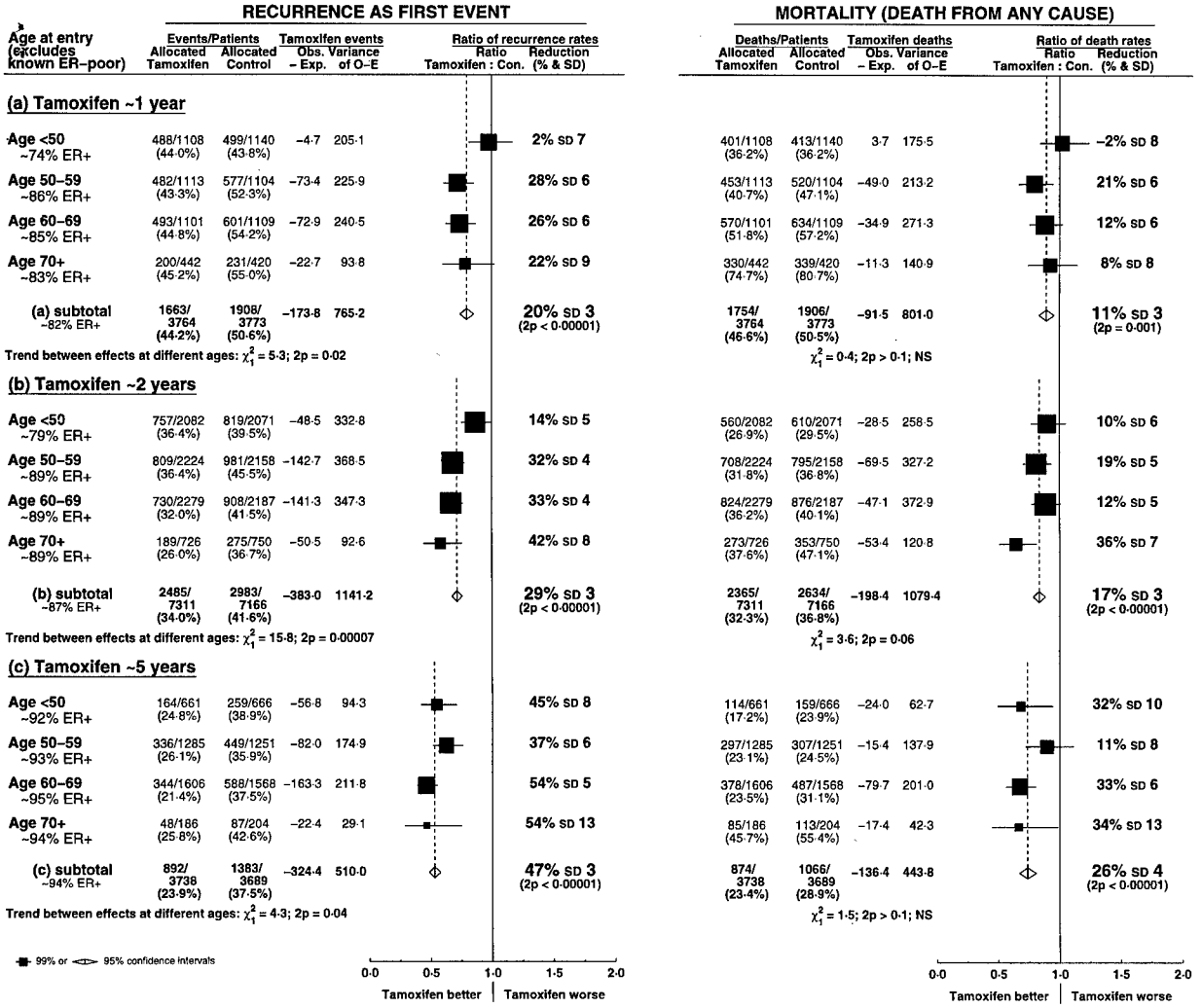

Figure 7: **Proportional risk reductions, subdivided by tamoxifen duration and by age when randomised (after exclusion of women with ER-poor disease)**
Tests for trend with respect to age are provided.

trials of 1 year of tamoxifen, and 14% longer in the trials of about 5 years of tamoxifen). Thus, the crude proportions of tamoxifen-allocated and of control-allocated women suffering these other outcomes cannot be compared directly, so the first two columns of data in table 2 relate the outcomes to the numbers of woman-years at risk rather than the numbers randomised. More exact allowance can be made by proper log-rank analyses and "survival-curve" calculations, and these are presented in the remaining columns of table 2.

Contralateral breast cancer incidence—In the trials of 1, 2, or about 5 years of tamoxifen, the proportional reductions in the incidence rate of contralateral breast cancer among women allocated tamoxifen were, respectively, 13% (SD 13; NS), 26% (SD 9; 2p=0·004), and 47% (SD 9; 2p<0·00001). Proportional reductions are calculated from table 2 as 100−100×ratio of rates. This tendency for the trials of longer tamoxifen duration to involve larger reductions in the incidence of new primary cancer in the opposite breast is significant (trend test χ^2_1=7·3, 2p=0·008), and these analyses indicate that about 5 years of tamoxifen approximately halves the annual incidence rate of contralateral breast cancer.

For contralateral breast cancer, the proportional risk reductions were approximately independent of age (age less than 50, 27% [SD 11] reduction; age more than 50, 31% [SD 7] reduction), as was the absolute annual incidence among the control-allocated women (which, taking all ages together, was 5 per 1000 [based on 485 cases in 95 300 years of follow-up], table 2). A quarter of the women in these trials are from Japan, where the national breast cancer rates are lower than in North America or western Europe,[8] and the annual incidence of contralateral breast cancer observed in the control-allocated women was 2 per 1000 in Japan and 6 per 1000 elsewhere. Hence, if the incidence of contralateral breast cancer really can be halved by about 5 years of tamoxifen, the absolute annual benefit would be about 1 per 1000 in Japan and 3 per 1000 elsewhere, both for younger and for older patients. The proportional reduction in contralateral breast cancer appeared to be about the same size in women with ER-poor tumours (29% [SD 15]) as in other women (30% [SD 6]).

Colorectal cancer incidence—Based on results from particular studies,[9] it has been suggested that tamoxifen might be associated with an increase in colorectal cancer.

Scheduled tamoxifen duration	Events/1000 years*		Tamoxifen		Ratio of rates (SD)	2-sided p (or NS)	10-year risk per 1000†		
	Allocated tamoxifen	Adjusted control	O−E	Variance of O−E			Tamoxifen	Control	Difference (SD)
Contralateral breast cancer incidence‡									
1 year	101/29·0	106/27·2	−6·9	50·8	0·87 (0·13)	NS	23	26	3 (4)
2 years	175/53·5	220/47·2	−27·7	91·4	0·74 (0·09)	0·004	21	28	7 (3)
~5 years	93/23·6	159/21·0	−39·1	62·0	0·53 (0·09)	<0·00001	26	47	21 (5)
Total	369/106·1	485/95·3	−73·6	204·2	0·70 (0·06)	<0·00001	23	32	9 (2)
Colorectal cancer incidence‡									
1 year	42/29·0	27/27·2	4·8	16·8	1·33 (0·28)	NS	9	7	−2 (2)
2 years	42/53·5	38/47·2	0·8	17·6	1·05 (0·24)	NS	5	5	0 (1)
~5 years	34/23·6	30/21·0	−0·3	15·7	0·98 (0·25)	NS	9	9	0 (2)
Total	118/106·1	95/95·3	5·3	50·1	1·11 (0·15)	NS	7	7	0 (1)
Endometrial cancer incidence‡									
1 year	23/28·9	10/27·2	5·7	8·2	2·2§	0·05	5	2	−3 (1)
2 years	26/55·4	13/48·9	4·9	9·5	1·8§	0·11	4	2	−2 (1)
~5 years	43/26·9	9/23·6	15·0	12·8	4·2§	<0·0001	11	3	−9 (2)
Total	92/111·2	32/99·6	25·6	30·5	2·58 (0·35)§	<0·00001	6	2	−4 (1)
Endometrial cancer mortality‡									
1 year	11/27·2	4/25·7	2·8	3·7	. .§	NS	2	1	−1 (1·0)
2 years	9/56·1	1/49·5	3·5	2·4	. .§	0·03	1	0	−1 (0·4)
~5 years	7/26·4	0/23·2	3·0	1·7	. .§	0·02	2	0	−2 (0·8)
Total	27/109·7	5/98·4	9·4	7·8	. .§	0·0008	1·7	0·4	−1 (0·4)
Death from a cause other than breast or endometrial cancer‡									
1 year	339/27·2	279/25·7	11·3	148·2	1·08 (0·09)	NS	77	73	−4 (6)
2 years	423/56·1	414/49·5	−15·7	190·9	0·92 (0·07)	NS	49	52	3 (4)
~5 years	228/26·4	193/23·2	1·4	101·7	1·01 (0·10)	NS	59	58	−1 (6)
Total	990/109·7	886/98·4	−3·1	440·8	0·99 (0·05)	NS	59	59	0 (3)

Includes all women, irrespective of ER status, in those trials with data on the relevant outcome.
*Tamoxifen delays recurrence, increasing the number of thousands of woman-years at risk; reduction of tamoxifen-allocated events by about 10% would approximately correct for this. The statistical analyses in columns 4–10, however, exactly correct for it.
†Since the women spend about two-thirds of the first 10 years alive and without recurrence, these 10-year risks are estimated as two-thirds of the Kaplan-Meier calculations of the 10-year risks if no other events had occurred. Comparisons between the ratios of rates in trials of different tamoxifen durations may be useful, but comparisons between the absolute risks may not be, since they are not standardised for age (or other risk factors).
‡With no prior recurrence of breast cancer recorded. The trend in the ratios of rates with respect to tamoxifen duration is significant for contralateral breast cancer (χ^2_1=7·3, p<0·008), but NS (p>0·1) for the other endpoints.
§Ratios of rates are not statistically stable and so, just for endometrial cancer incidence, are estimated from events/1000 years. The available data are inadequate to estimate ratios for endometrial cancer mortality.

Table 2: **Effects of treatment allocation on selected outcomes**

Overall, however, in the present overview of results from all trials (including those that generated this hypothesis), there was only a slight and non-significant excess of colorectal cancer among women allocated tamoxifen (ratio of incidence rates 1·11 [SD 0·15]; NS). The apparent excess was larger (though still not significant) in the trials of just 1 year of tamoxifen (ratio 1·33 [SD 0·28], NS), and there was no apparent excess in the trials of 2 years (ratio 1·05 [SD 0·24], NS) or about 5 years (ratio 0·98 [SD 0·25], NS) of tamoxifen. None of these results is statistically significant, and because the apparent excess was almost entirely confined to the trials of only 1 year of treatment, the available randomised evidence does not indicate that tamoxifen produces any increase in colorectal cancer (although the CIs for the ratios are wide).

Endometrial cancer incidence—By contrast, the overall increase in the incidence of endometrial cancer was highly statistically significant (ratio of incidence rates 2·58 [SD 0·35]; 2p<0·00001). Since this estimate is based on a total of only 32 cases among control-allocated women, the separate ratios of rates for the trials of 1, 2, and about 5 years of tamoxifen cannot be estimated reliably. So, although the approximate ratios of 2·2, 1·8, and 4·2 in these three groups of trials suggest that 1 or 2 years of tamoxifen approximately doubles the incidence of endometrial cancer and that 5 years of tamoxifen approximately quadruples it, these ratios are not significantly different from each other. Similar ratios of rates of endometrial cancer were observed in trials of 20 mg and 30–40 mg tamoxifen daily (2·7 and 2·4, respectively). Although these findings involve only limited numbers of endometrial cancers, they are reinforced by epidemiological studies that involve large numbers.[10] In the general population, the annual incidence rate of endometrial cancer during the mid-1980s at ages 55–84 was 0·1 per 1000 in Japan but 1·0 per 1000 in the USA, with the rates in Europe about half those in the USA.[8] The relative risks appeared to be similar in the Japanese trials and in the other trials in the overview, but the absolute risks in the control-allocated women did not, being 0·1 and 0·4 per 1000 per year, respectively. Hence, if the relative risk associated with tamoxifen is about the same in different populations, the absolute risks will differ substantially.

Even in the trials of about 5 years of tamoxifen, the absolute increase in endometrial cancer was only about half as big as the absolute decrease in contralateral breast cancer. The three largest such trials (Stockholm B,[9,11] Scottish,[12] and NSABP B14[13]), which were conducted in Europe or North America, provided data on the incidence of both contralateral breast cancer and endometrial cancer. In the aggregate of these three large trials, allocation to about 5 years of tamoxifen was associated with 33 more cases of endometrial cancer (42 during 24 000 woman-years of follow-up in the tamoxifen groups *vs* nine during 21 200 woman-years in the control groups), but 66 fewer cases of contralateral breast cancer (91 *vs* 157).

Endometrial cancer mortality—Of 124 women who developed endometrial cancer, 18 died with breast-cancer recurrence reported and 40 died without it (29 with death attributed to endometrial cancer, three deaths probably due to the disease, and eight deaths not due to breast or endometrial cancer). Overall, there were 27 endometrial cancer deaths (including the three probable such deaths)

among women allocated tamoxifen and five among those not (2p=0·0008). This total does not include any of the 18 deaths after recurrence of breast cancer had been reported, because most such deaths are likely to have been due to breast cancer. (The mortality analyses in figures 1–7, however, include all deaths, irrespective of their cause.)

The absolute excess of deaths from endometrial cancer during the whole decade after randomisation was, in each of the three tamoxifen duration categories, about 1 or 2 per 1000 (corresponding to an annual excess of about 0·2 per 1000). There was a non-significant tendency for the excess of endometrial cancer deaths to be greater in the trials of longer durations of tamoxifen. Although this trend may well be real, the absolute excess was not large. Among 3673 women allocated about 5 years of tamoxifen in trials that provided cause-of-death information, there were seven endometrial cancer deaths during 26 400 woman-years of follow-up before any recurrence of breast cancer, and the cumulative risk during the whole of the first decade was about 2 deaths from endometrial cancer per 1000 (95% CI about 0 to 4 per 1000).

Causes of death other than breast or endometrial cancer—The underlying causes of those deaths that were specified not to be due to breast cancer (and had not been preceded by any recorded recurrence of breast cancer) were subdivided into ten categories: endometrial cancer, other neoplastic, cardiac, cerebrovascular, pulmonary embolus, other vascular, respiratory, infective, other medical, and non-medical causes. The difference in non-breast-cancer mortality between tamoxifen and control was significant for endometrial cancer (table 2) but not for any of the other nine categories separately (each 2p>0·1), or for the aggregate of all cardiac or vascular deaths (2p>0·1), or for the aggregate of all non-breast, non-endometrial-cancer deaths (death rate ratio 0·99 [SD 0·05], 2p=1·0; bottom line of table 2). About one extra death per 5000 woman-years of tamoxifen was attributed to pulmonary embolus, but this excess was not statistically significant.

Tamoxifen has been shown to reduce blood concentrations of low-density-lipoprotein cholesterol by about 20%,[14] and, in other circumstances, such cholesterol reductions maintained for about 5 years reduced coronary-heart-disease deaths by about 15%, with smaller reductions in other vascular deaths.[15] In the trials of about 5 years of tamoxifen, however, only 203 deaths were attributed to vascular causes other than pulmonary embolus and so reductions of 10–15% could not be reliably detected or refuted (death rate ratio 1·02 [SD 0·14]).

Long-term administration of high doses of tamoxifen has been associated with an increased incidence of hepatomas in some, but not other, laboratory animals.[16] In these trials, however, women allocated tamoxifen had slightly fewer deaths attributed to liver disease than women in the control groups (non-neoplastic, nine tamoxifen *vs* 12 control; primary liver cancer, three *vs* seven). Based on 1990 west European or North American death rates,[17] the expected number of deaths from liver cancer in the control group would be about four. One-quarter of the patients were from Japan, where the national death rates from liver cancer are high,[8] but neither in Japan (zero tamoxifen *vs* three control) nor elsewhere (three *vs* four) was any excess of liver cancer deaths recorded in the tamoxifen-allocated women in these trials.

Discussion

This collaboration has now continued for over 10 years, accumulating more randomised evidence on tamoxifen than is available on any other anticancer drug, and these updated results are essentially complete (table 1). What is new is the growing evidence for the importance of the hormone-receptor measurement as a determinant of the response to treatment, the widening range of patients for whom some years of adjuvant tamoxifen is now known to be protective (including those aged under 50), the strength of the indirect evidence that about 5 years of adjuvant tamoxifen is more effective than shorter durations of treatment (particularly after long follow-up), the definiteness of the evidence on contralateral breast cancer and endometrial cancer, and the evidence of safety with respect to other causes of death. Among women with ER-positive tumours (or those for whom no receptor measurement is available), a few years of adjuvant tamoxifen treatment is of net benefit not only for those with node-positive disease but also for those with node-negative disease (figures 3 and 4), and, even if cytotoxic chemotherapy has been given, some years of adjuvant tamoxifen produces additional benefit (figure 6). Adjuvant tamoxifen can produce substantial benefit not only for women aged 50–69 and those aged 70 or more but also, in contrast with earlier reports,[1-3] for those aged under 50 (figure 7).

Hormone receptors

ER-positive (or ER status unknown)—The apparent benefits of tamoxifen for women whose tumours were classified as ER-positive are still about as great as in the previous cycle of this collaboration.[3] Figure 2 shows that, for all tamoxifen durations taken together, the recurrence reduction among women with known ER-positive tumours is now 34% (SD 3) compared with 32% (SD 3) previously, and the mortality reduction is now 20% (SD 3) compared with 21% (SD 3) previously. There was no evidence in these trials that a negative PR assay could identify a non-responsive subset of women with ER-positive tumours. Moreover, even if an ER assay had not been done or the assay result was uncertain (ER unknown in figure 2), the benefits of tamoxifen were about three-quarters as great as for women with known ER-positive tumours. So, whereas a false-positive ER assay is unlikely to produce net hazard (especially since a few years of tamoxifen appears to produce a reduction in the risk of contralateral breast cancer that is bigger than any increase in the risk of endometrial cancer) unless it leads to other treatments being inappropriately withheld, a false-negative ER assay that led to tamoxifen being withheld could be seriously disadvantageous. Apparently negative ER assay results should therefore be considered carefully, and perhaps repeated, either by the same or by a different method.[18] The definition used to distinguish ER-positive from ER-negative tumours may also be important because some studies suggest that even women with tumours that contain very low but still detectable amounts of the receptor protein may still benefit from tamoxifen,.[7,18]

ER-poor tumours—By contrast, there is no clear evidence of benefit in women whose tumours were classified as ER-poor. Figure 2 shows that, for all tamoxifen durations taken together, the proportional recurrence reduction among such women is now only 10% (SD 4) compared

with 13% (SD 4) previously, or 9% (SD 4) if contralateral breast cancers are not included, and the proportional mortality reduction is now only 6% (SD 4) compared with 11% (SD 5) previously. Moreover, even if consideration is restricted to the trials of about 5 years of tamoxifen, which appeared to be a particularly effective regimen for women with ER-positive tumours, there was no apparent effect on recurrence or mortality among women with ER-poor tumours (figure 2). For all tamoxifen durations taken together among such women, there was no significant heterogeneity between the effects of tamoxifen in the absence of chemotherapy (14% [SD 7] recurrence reduction; 8% [SD 7] mortality reduction) and in the presence of chemotherapy (8% [SD 5] recurrence reduction; 4% [SD 5] mortality reduction). There was some suggestion that a positive PR assay might identify a tamoxifen-responsive subset of those with ER-poor tumours, but the number of women studied was too small for this finding to be trustworthy. Similarly, although there appeared to be somewhat greater effects among women with ER-poor tumours who were aged 50 or older at randomisation (16% [SD 5] recurrence reduction; 12% [SD 5] mortality reduction), these results are not clearly different from the overall findings for women with ER-poor tumours, and data-dependent emphasis on these results just among older women may be misleading.

Thus, whereas the overall benefits of a few years of adjuvant tamoxifen for women with ER-positive disease are substantial and definite, those for women with disease that has been reliably shown to be completely without any functional hormone receptor are not, and remain a matter for research. Although allocation to tamoxifen produced a slight reduction in the non-contralateral breast cancer recurrence rates among women whose original tumour was classified many years ago as ER-poor, this finding may represent benefit just in those women whose tumour would have been classified as ER-positive by more sensitive methods. In that case, the chief benefit to be expected among those women with truly ER-negative tumours would be a reduction in the incidence of contralateral breast cancer, against which must be set a real, though smaller, increase in endometrial cancer. On the other hand, if there are some small, but still real, beneficial effects of tamoxifen on recurrence among women whose tumours are reliably shown to be ER-negative, this effect would be of both practical and theoretical importance.

Duration of adjuvant tamoxifen

5 years versus shorter—After exclusion of women considered to have ER-poor tumours in these trials, the difference between the recurrence reductions associated with 5 years and with only 1 or 2 years of adjuvant tamoxifen was large, and did not appear to be accounted for by differences in nodal status, tamoxifen dose, concurrent chemotherapy, age, or menopausal status (figures 3, 6, and 7). This finding therefore strongly suggests that about 5 years of adjuvant tamoxifen produces a substantially greater delay of recurrence than is produced by just 1 or 2 years of treatment. This conclusion is consistent with the recently reported results of two directly randomised comparisons of 5 years versus 2 years of adjuvant tamoxifen,[19,20] in which longer treatment yielded a 21% (SD 7) further reduction in recurrences during the first few years after randomisation (373 [11·6%] recurrences among 3211 allocated 5 years *vs* 469 [14·3%] among 3271 allocated 2 years of tamoxifen; $2p<0·001$). Similar findings have also been reported in abstract from the French TAM-01 trial of lifelong tamoxifen versus 2–3 years of tamoxifen.[21]

For mortality, there was also a significant trend ($2p=0·003$) towards a greater benefit with longer tamoxifen treatment (figure 3), although the difference in the sizes of the proportional risk reductions was less extreme than was the case for recurrence. Similarly, in the published direct randomised comparisons of 5 versus 2 years of tamoxifen,[19,20] the difference for breast-cancer deaths (6·9% *vs* 8·5%, $2p=0·02$) is less extreme than that for recurrence. Judgments may differ as to how strong the evidence now is on whether 5 years of adjuvant tamoxifen produces a greater survival advantage than shorter regimens, especially if those who relapse then get tamoxifen. Substantially larger amounts of evidence from directly randomised comparisons of 5 years versus shorter durations of adjuvant tamoxifen will, however, be available for central review in the year 2000.

5 years versus longer—The present review has not addressed the question of whether giving adjuvant tamoxifen for more than 5 years would produce any worthwhile additional benefits, and it may well take at least another decade for this question to be answered reliably.[22] Both the adverse and the protective long-term side-effects are likely to be greater with longer treatment. For example, trials of continuing for another 5 years after completion of 5 years of adjuvant tamoxifen might well involve two-fold further differences in the incidence of endometrial cancer and of contralateral breast cancer (table 2). In Europe or North America, this effect would be expected to yield an absolute increase of about 1% in endometrial cancer and an absolute decrease of about 1% in contralateral breast cancer. If so, the balance of risk and benefit would be determined chiefly by the effect of the additional treatment on the long-term recurrence rate of the original breast cancer. One potential difficulty for such trials is the possible carry-over benefit of adjuvant tamoxifen, whereby 5 years of adjuvant tamoxifen produces a substantial protective effect not only while it is being taken but also during the next 5 years (figure 5). Hence, even if 10 years of adjuvant tamoxifen is importantly better than 5 years of adjuvant tamoxifen, this advantage may not become substantial until well after year 10. Results to about year 10 have recently been reported from three such trials,[23-25], with no evidence of early benefit, but this follow-up may well have been far too short.[22] Moreover, since these three trials have together randomised only 1700 women (mostly with node-negative disease), they involve a total of only about 100 breast cancer deaths, which is far too few. Thus, the currently available trial results still leave substantial uncertainty[22] as to whether treatment should routinely continue beyond 5 years.

Age

The lack of definite benefit among younger women in the previous overviews[1-3] may have been due partly to the play of chance (which, particularly in trials of only 1 or 2 years of treatment, could obscure any real benefits) and partly to the higher prevalence of ER-negative disease in younger women. With the larger numbers now available, it is clear that about 5 years of adjuvant tamoxifen has a

substantial effect on recurrence and on long-term survival not only in older women but also in younger women (figure 7). Moreover, the substantial benefits of adjuvant ovarian ablation on long-term survival in women under the age of 50 that have recently been demonstrated[5] provide further evidence of the importance of adjuvant hormonal therapy for many premenopausal breast cancer patients. Hence, neither youth nor age should be a barrier to the use of tamoxifen in women with ER-positive tumours (or in those with no ER measurement available).

Addition of tamoxifen to chemotherapy

Irrespective of whether—in comparison with the trials of tamoxifen on its own—there were greater or lesser treatment effects in the trials of tamoxifen plus chemotherapy versus chemotherapy alone, the addition of tamoxifen to chemotherapy certainly produced some additional benefits. In particular, chemotherapy plus about 5 years of tamoxifen was substantially better than the same chemotherapy alone. (The assessment of whether chemotherapy adds to the benefits of tamoxifen in different settings will be the subject of a subsequent report.) Many forms of chemotherapy or radiotherapy might be more effective in the absence of a drug, such as tamoxifen, that slows the division of the cancer cells that these treatments would otherwise have attacked. So, although no large directly randomised comparisons of concurrent versus consecutive chemoendocrine therapy are yet available, it might be better to delay the start of any hormonal treatment until after any radiotherapy or chemotherapy has been completed, especially if these treatments last only a few months. But, even definite plans to give certain such women radiotherapy, chemotherapy, or both, without concurrent tamoxifen should not preclude the subsequent use of adjuvant tamoxifen.

Conclusions

The fundamental question when assessing the proportional risk reduction that a woman can expect from a few years of adjuvant tamoxifen is whether her tumour is completely ER-negative—and not whether she is young or old, with or without nodal involvement, or receiving chemotherapy. If the tumour is shown by reliable assays to be completely ER-negative, although adjuvant tamoxifen might produce some small but still clinically meaningful benefit (figure 2), it might well not do so: further research is needed. If, however, the tumour has detectable ER, then adjuvant tamoxifen, perhaps for about 5 years, should generally produce benefits about as great as in the lower part of figure 4, largely irrespective of age, previous chemotherapy, or menopausal status—and, even if hormone-receptor measurements are not available, a substantial fraction of these benefits can still be expected. The absolute benefits at 10 years would, however, be substantially smaller for women with an extremely good prognosis, such as those with small localised tumours of good histological grade, which can nowadays be found by screening programmes.

Figure 4 may underestimate the real benefits of actually giving long-term adjuvant treatment to women whose tumours are definitely ER-positive, because it does include some women who did not have ER-positive tumours, and because there is an appreciable amount of non-compliance with the allocated treatment. For example, about 20% of women allocated about 5 years of adjuvant tamoxifen in the three largest trials[11-13] (which contribute about three-quarters of the data on such regimens) either failed to start it or discontinued it prematurely; in addition, a few of those allocated control received some adjuvant tamoxifen. Due allowance for this non-compliance would increase the estimated benefits. But, if tamoxifen had been given to all women in the control groups who relapsed, the overall survival difference might have been lessened. It would probably not, however, have become much smaller, for although in two of the three large trials of prolonged tamoxifen only about half the patients got such treatment on recurrence,[11,13] the third such study was the Scottish trial,[12] in which almost all did so (and, the 99% CI for that trial still shows a substantial survival improvement: figure 1).

Trials of ovarian ablation began half a century ago[5] and trials of tamoxifen began a quarter of a century ago, yet in the early 1980s hormonal adjuvant therapy was still greatly undervalued. Since then, receptor assays have improved, tamoxifen regimens have become longer, and there have been substantial increases in the total numbers of randomised women, in the duration of follow-up of the trials and, through the present collaboration, in the public availability of the randomised evidence. It is now clear that, at least for women whose primary tumours have functional ER, effective hormonal treatment is of substantial value. This report makes no recommendations as to who should or should not be treated, because treatment decisions involve not only survival and cancer recurrence but also factors that have not been reviewed, such as costs and symptomatic side-effects (which, to avoid bias, should preferably be assessed by review of the placebo-controlled trials).[26] At least in terms of recurrence and survival, however, the balance of the known long-term benefits and risks strongly favours some years of adjuvant tamoxifen for a wide range of women with early breast cancer.

Early Breast Cancer Trialists' Collaborative Group

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APPENDIX 2

potentially valuable model to study the biologic differences within the ovaries of women at increased risk of developing ovarian cancer and the ovaries of women without increased risk. It is quite likely that the biologic mechanisms of the development of ovarian cancer in sporadic cases is similar to the mechanisms of development in women with genetic predisposition to develop the disease. The elucidation of these biologic mechanisms will allow rational approaches to the diagnosis, treatment, and, most important, prevention of this deadly disease.

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Note

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Five Years of Tamoxifen—or More?

*Richard Peto**

Before 1990 there had been, for half a century, little evidence of any decrease in the U.S. age-standardized death rate from breast cancer. Chu et al. (*1*), however, have recently described a sudden decrease in breast cancer mortality during the 1990s, which they ascribe to the combined benefits of early detection and better treatment (particularly adjuvant chemotherapy and hormonal therapy) during the 1980s. A decrease during the 1990s relative to the previous pattern of U.S. breast cancer mortality is seen in each decade of age from 30-39 years to 70-79 years. In Britain, where there had been much less mammography during the 1980s but perhaps even more adjuvant hormonal therapy, a similarly sudden decrease in breast cancer mortality has also been seen during the 1990s, and at least some of this decrease is also attributable to better treatment of the disease, particularly with tamoxifen (2).

Although the absolute benefit produced by a few years of adjuvant tamoxifen therapy for patients with early breast cancer is not large (50% survival might, for example, be increased to 55% or 60%), the treatment is widely practicable and the disease is common. Since about one million women worldwide are now taking tamoxifen, this drug may well be preventing more cancer deaths than any other. But there is still widespread uncertainty as to how long such adjuvant therapy should usually continue. This question is being addressed directly by several trials that randomly assign women to different durations of adjuvant tamoxifen therapy (e.g., 2 versus 5 years or 5 versus 10 years). Last month and this month in the Journal, preliminary results have been reported from four of these trials (*3-6*). One of the reports, i.e., the one from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (*6*), also includes some of the best evidence ever published on the advantages of 5 years of adjuvant tamoxifen versus no adjuvant tamoxifen, finding highly significant delays in disease recurrence both for women who were under 50 years of age when they were randomly assigned and for older women.

The original trials of adjuvant tamoxifen versus control that began in the 1970s quickly showed that both local and distant recurrences could be delayed. However, when distant recurrence occurred in those women who had not been allocated to adjuvant tamoxifen, then hormonal treatment would often be used to try to delay its progress. Since the additional recurrences in the control groups were those that could have been delayed if tamoxifen had been given initially, many of them could still respond to hormonal treatment. Thus, as far as survival is concerned, many of these studies should be thought of not as trials of tamoxifen versus no tamoxifen but rather as trials that compared two different strategies for using tamoxifen (i.e., as trials of adjuvant tamoxifen versus tamoxifen only when recurrence occurred). Hence, especially in the first few years after randomization in these studies, the effect of adjuvant tamoxifen on survival was less extreme than its effect on recurrence and was less quickly recognized. Indeed, in the early 1980s, it was widely, though mistakenly, believed that the previous trials had proved that adjuvant tamoxifen did not affect survival.

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By 1984, however, a preliminary meta-analysis showed some effect on survival (*7*), and more detailed meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 1985 showed that 5-year survival could be improved (*8*). In 1985, however, it was only the overall results from the 28 trials then available (total at that time: 1762 deaths with adjuvant tamoxifen therapy versus 2020 without, two-sided $P<.00001$) that were statistically reliable. Although there was no significant heterogeneity in the results from the 28 trials in the 1985 overview, the play of chance meant that there was still, at that time, no apparent benefit in some of the studies (including, as it happened, the largest of them, which was the NSABP B-09 trial, then with 359 versus 363 deaths).

By the time of the 1990 EBCTCG overview (*9*), with more trials and longer follow-up, it had become apparent that the absolute survival advantage was greater after 10 years than after only 5 years of follow-up and that the benefit appeared to be greater with more prolonged tamoxifen treatment. Most of the trials of adjuvant tamoxifen therapy versus control (again, "control" might well mean "no tamoxifen unless disease recurrence is diagnosed") involved only 1, 2, or 5 years of adjuvant tamoxifen therapy. Within this range, more prolonged treatments appeared to be more effective at preventing or delaying recurrence and improving 10-year survival. Hence, when tamoxifen is being used as an adjuvant therapy for early breast cancer, many doctors now recommend that it should continue for about 5 years, and there have been suggestions that it should, for certain patients, continue for 10 years or even indefinitely.

But tamoxifen does have some adverse side effects that must be expected to be aggravated by longer treatment; perhaps the most important of these is an increased incidence of endometrial cancer (which, with only a few years of treatment, causes about one extra death per thousand women). Although, in terms of survival, the benefits of tamoxifen therapy are far greater than the hazards, there continues to be much debate as to whether a shorter duration of adjuvant tamoxifen (e.g., 2 years) might suffice and, conversely, as to whether a longer duration (e.g., 10 years) might generally be preferable. This question is important because, with about one million women now taking tamoxifen, even a small further improvement in long-term survival might prevent several thousand deaths a year.

It is, however, a surprisingly difficult question to answer directly because there is a substantial "carry-over" benefit from tamoxifen that lasts well beyond the treatment period. Thus, a few years of adjuvant tamoxifen therapy produces a reduction in the annual recurrence rate (and in the annual death rate) not only while treatment continues but also for some years after the treatment has ended (*6,8*). This persistent benefit was helpful in the trials of a few years of tamoxifen therapy versus no adjuvant tamoxifen, since it increased the difference in 10-year survival between treatment and control groups. However, in trials that compare stopping after just a few years of tamoxifen versus continuing for several additional years, this carry-over benefit may initially be an obstacle, since a persistent benefit in the control (i.e., shorter duration) group may mean that, for the first few years of additional treatment, there is little additional benefit, even if later on a worthwhile additional benefit will emerge. Thus, trials of 2 versus 5 years of tamoxifen therapy may well need 10 years of follow-up rather than 5, and trials of 5 versus 10 years of therapy may well need 15 years of follow-up after the initial diagnosis rather than 10.

Even more than was the case with the trials of adjuvant tamoxifen versus control, what may be needed in the trials of a few years versus several years of adjuvant tamoxifen therapy is randomization of a total (in all trials) of some tens of thousands of women, many years of follow-up, and, finally, worldwide collaboration in the interpretation of the overall findings. Nevertheless, the early results from the four newly published trials (*3-6*) are still of substantial interest (Table 1).

The two European trials (*3,5*) both compared 2 versus 5 years of adjuvant tamoxifen. Both trials involved substantial numbers of recurrences (British trial: 335; Swedish trial: 507) and of deaths (British trial: 204; Swedish trial: 294), both found significantly fewer recurrences with 5 years than with 2 years of tamoxifen therapy (British trial: two-sided $P<.05$; Swedish trial: two-sided $P<.01$), and both found somewhat fewer deaths with 5 years than with 2 years of treatment. These promising mortality differences, however, are not at present statistically convincing.

The two North American trials (*4,6*), one from the Eastern Cooperative Oncology Group (ECOG) and the one from the NSABP, both compared 5 versus about 10 years of adjuvant tamoxifen. The numbers of recurrences after these randomizations were relatively small (ECOG trial: 38; NSABP B-14 trial: 53), as were the numbers of deaths after recurrence (ECOG trial: 16; NSABP B-14 trial: 25). The NSABP results favor 5 years of

Table 1. Results from four new trials of different durations of adjuvant tamoxifen therapy for early breast cancer*

	Swedish trial (*5*)		British trial (*3*)		NSABP B-14 trial (*6*)		ECOG trial (*4*)	
	2 y of therapy	5 y of therapy	2 y of therapy	5 y of therapy	5 y of therapy	10 y of therapy	5 y of therapy	10+ y of therapy
No. of women randomly assigned	1801	1744	1470	1467	570	583	93	100
No. of breast cancer recurrences	279	228	190	145	19	34	23	15
No. of deaths after recurrence or from an unknown cause	162	132	110	94	9	16	8	8
No. of deaths from a known cause before recurrence	92	78	14	18	5	9	2	6

*The women randomly assigned are those apparently free of breast cancer 2 years (*3,5*) or 5 years (*4,6*) after diagnosis, and the recurrences reflect the numbers of these women with a subsequent diagnosis of distant, local, or contralateral breast cancer. NSABP = National Surgical Adjuvant Breast and Bowel Project; ECOG = Eastern Cooperative Oncology Group.

treatment rather than 10, while the ECOG results suggest the opposite (Table 1). Neither set of results, however, is statistically convincing on its own, especially since the public availability of the results has been influenced by the patterns that they suggest.

Both in the meta-analysis of the trials of adjuvant tamoxifen versus control (*9*) and in these four trials of one adjuvant duration of tamoxifen versus another (*3-6*), there is no good evidence that any causes of death other than breast cancer or endometrial cancer are affected by tamoxifen. (The slight excess of other deaths in some of the trials of 5 years versus longer is not significant and involves many different causes.)

A formal meta-analysis of these four trials of different tamoxifen durations is not appropriate. First, there are several other trials of about 2 versus 5 years of tamoxifen plus one other trial [from Scotland (*10*)] of 5 years versus longer. Second, the NSABP B-14 results are available only because they led the trial to be interrupted by its data-monitoring committee. The chief reason, however, is that the follow-up is not yet long enough, and the early findings in such trials may be therapeutically misleading. The carry-over effect (i.e., the reduction in the annual recurrence rate not only while tamoxifen is being taken but for a few more years as well) means that the balance of risk (e.g., of endometrial cancer) and benefit (e.g., of long-term survival) may change with longer treatment.

At their 1995 meeting, the Early Breast Cancer Trialists agreed that the trials of tamoxifen duration were not yet sufficiently mature to be reviewed, but a systematic worldwide review of all such trials would be appropriate in the year 2000. In retrospect, therefore, it may have been unwise for the 1995 National Cancer Institute (NCI) clinical announcement (*11,12*) of the NSABP B-14 and Scottish trial results to have concluded so definitely that 5 years of treatment is enough, especially since the NSABP B-14 results had been made available by the Data-Monitoring Committee only because they appeared to be unfavorable, while the apparently favorable ECOG results remained concealed from the NCI. (If the NCI claims of hazard were justified, then one would have expected an adverse trend in the ECOG results as well, whereas, in fact, the ECOG data tend, if anything, to favor more than 5 years of treatment.)

Both direct (*3,5*) (*see* Table 1) and indirect comparisons do suggest that 5 years of adjuvant tamoxifen treatment is more promising than just 2 years of such treatment, although, for this comparison, a definitive conclusion about long-term survival may not be possible until at least the year 2000. But neither direct nor indirect comparisons can yet address the question of whether substantially more than 5 years of adjuvant tamoxifen treatment will yield better long-term survival. Longer follow-up of the NSABP B-14, the ECOG, and the Scottish trials will help, but much larger numbers of patients still need to be randomly assigned. If the trials of different tamoxifen durations that are currently recruiting new patients can achieve really large-scale recruitment before the year 2000, then they will yield preliminary findings in 2005 and reliable findings in 2010.

Until then, the four new trial results (*3,6*) will tend to foster agreement with the statement in the summary of the NCI clinical announcement, "While we eagerly anticipate the results [of ongoing trials of 5 years versus longer], all available evidence indicates that 5 years of tamoxifen is a reasonable standard for the adjuvant setting." But they should also foster the continuing disagreement as to whether or not longer treatment is promising, which will probably be resolved only by long-term follow-up of substantially larger numbers of patients than those in the existing trials. This process is frustratingly slow, but eventually it is reliable, and it needs to be. 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.

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APPENDIX 3

THE LANCET

Variation in use of adjuvant tamoxifen

Christina Davies Paul McGale
Richard Peto

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Variation in use of adjuvant tamoxifen

Christina Davies, Paul McGale, Richard Peto

In 1997, we asked about the prescription of adjuvant tamoxifen for breast cancer by medical opinion leaders in continental Europe, Asia, South America, and Australasia. We defined an opinion leader by attendance at international meetings or interest/participation in clinical trials. Our survey was not intended as a random sample of doctors or patients, but the qualitative findings are of substantial relevance.

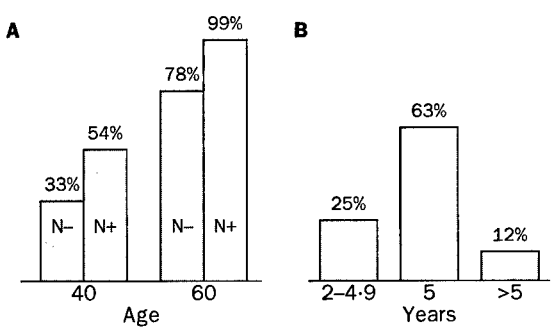
Questionnaires were sent twice to 3000 doctors, asking whether they treated breast cancer and, if so, whether they usually used adjuvant tamoxifen in women aged 40 years (premenopausal) or 60 years (postmenopausal) with (N+) or without (N-) local lymph-node involvement. The questionnaire also asked how long they would usually continue such treatment. 1053 replied, including 841 who treat breast cancer. Of 1947 non-responding addressees, we telephoned a random sample of 50: 62% were doctors who treat breast cancer and could have replied.

Among those who treat breast cancer, the replies indicated wide variation in prescribing practice. However, the overall percentages with particular prescribing patterns were similar for respondents from different regions, for the randomly telephoned non-respondents and for each of the different specialties dealing with breast cancer. Almost all these breast-cancer doctors (99%) would generally use tamoxifen in older women with N+ disease, but only half (54%) would do so in younger women with N+ disease. These percentages were smaller (78% and 33%, respectively) for women with node-negative disease (figure, A).

Although age and, to a lesser extent, nodal status strongly affect whether adjuvant tamoxifen is prescribed, they had little effect on the usual duration of the regimen used which, for 75% of these doctors, was at least 5 years (figure, B). 12% of clinicians used a longer regimen, however, indicating that a significant minority of these opinion leaders hope for additional benefit from continuing tamoxifen beyond the initial 5 years. That may be justified, but such continuation still needs reliable assessment.[1]

As the evidence from the randomised trials of adjuvant tamoxifen continues to evolve,[2-4] patterns of tamoxifen use will continue to change. The trials, as summarised by the most recent quinquennial worldwide review,[4] now show that, at least for women with some oestrogen-receptor protein detectable on their primary tumour (and for women with no oestrogen-receptor assay done), about 5 years of tamoxifen substantially delays recurrence and improves 10-year survival. This is true not only for older women but also for younger women, irrespective of nodal status. Hence, if the general willingness to use tamoxifen for postmenopausal women with N+ disease were to be extended to those with N- disease, and to younger women, many more deaths could be avoided. Even for those who receive chemotherapy as part of their adjuvant treatment, addition of tamoxifen confers extra benefit.[4]

More than a million women worldwide are now prescribed tamoxifen, but the present heterogeneity in practice is disturbing, particularly with respect to the treatment of younger women (among whom only half of the respondents in our survey would use tamoxifen).



Patterns of adjuvant tamoxifen use

A: Effect of age and lymph-node involvement on percentage of breast-cancer doctors who would routinely consider adjuvant tamoxifen.
B: Usual duration of any adjuvant tamoxifen (percentage of doctors, not patients).

We thank the clinicians who responded. Helen Monaghan, Alison Naughten, and Abigail Headon coordinated the survey.

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APPENDIX 4

Appendix 4

Responsibilities of the International Coordinating Centre in Oxford

The following ongoing tasks are undertaken by the international coordinating centre in Oxford under the direction of Professor Richard Peto (RP) and Dr Christina Davies (CD):

- Preparation of the trial materials for individual countries and coordination of their supply and distribution to participating centres (now largely completed).
- Establishing and maintaining a central trial database with details of participating clinicians and individual patient data.
- Design and maintenance of the computer programs.
- Provision of a 24-hour randomization facility.
- Coordination of central data collection, validation, entry and analysis.
- Coordination of the supply and distribution of free tamoxifen provided by Zeneca Pharmaceuticals to participating centres that require it for ATLAS patients allocated to continue treatment for the next 5 years (see below).
- Liaison with National Coordinators and collaborators in each centre, and organization of meetings at national, regional and local levels, as appropriate. Coordination of, liaison with, and provision of administrative and scientific support to, as appropriate, individual partners (ATLAS National Coordinators), and fostering and strengthening the collaborative network.
- Organization of short-term visits of national coordinators to Oxford to provide training in trial methodology and to resolve any particular issues which arise in the implementation of ATLAS at a national level.
- Preparation of reports of the trial results for publication, and seeking comments from all collaborators prior to its revision and publication in the names of all participants.
- Organization of the rapid and wide dissemination of these results.

Organization of the supply and distribution of free tamoxifen

As described in previous reports to the US Army, it has been necessary to provide free supplies of tamoxifen in some countries. CD and RP were responsible for securing free Nolvadex from Zeneca Pharmaceuticals plc for those patients randomized in ATLAS to continue treatment for the next 5 years. The coordination of the packaging, labelling and distribution of appropriate amounts of tamoxifen to collaborating centres has been a major initiative managed by the coordinating centre in Oxford. Special computer programmes have been required to calculate the amount of tamoxifen needed on a per centre basis, and to ensure that centres always have sufficient supplies. Records of the batch of tablets distributed to particular centres are required, in case, for any reason, a particular batch needs to be recalled. Different countries have different regulations for packaging and importation of free drug supplies, and it has been necessary to fulfil the varying requirements. In each country, a tamoxifen coordinator has been appointed - usually the national coordinator for ATLAS within that country. Sufficient tamoxifen is sent for the entire country to the tamoxifen coordinator on a 6-monthly basis, and the coordinator is then responsible for distribution to individual hospitals within that country according to instructions from Oxford. Shipments are sent in January and July of each year, and it is anticipated that the free provision of drug will allow rapid randomization in particular countries. **N.B. The design and management of ATLAS remain entirely independent of the pharmaceutical company involvement to ensure that no suggestion of lack of objectivity of the findings can be made.**

APPENDIX 5

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APPENDIX 6

Reliable assessment of the efficacy and safety of prolonging the use of adjuvant tamoxifen: a large, simple, randomised study.

Adjuvant tamoxifen therapy in early breast cancer: Existing evidence

Trials of adjuvant tamoxifen in women with early breast cancer have demonstrated a highly significant improvement in 10-year survival. However, it is not yet known how long women with early breast cancer should continue to take adjuvant tamoxifen. Most trials of tamoxifen versus no tamoxifen involved only 1, 2 or 5 years of tamoxifen. Within this range, the more prolonged treatments appear more effective at preventing or delaying recurrence and improving 10-year survival. **However, among women who have already had some years of treatment there is no reliable evidence, from direct randomised comparisons of different durations, of an extra therapeutic advantage from more prolonged treatment.** Moreover, while tamoxifen has relatively few short-term or medium-term side-effects (particularly for post-menopausal women), it produces some increase in the incidence of endometrial cancer, and may have some other important long-term side-effects. These risks may increase if the drug is taken for many years. Hence, the balance of benefits and risks of long-term tamoxifen needs to be determined reliably.

If longer tamoxifen improved survival by just a few percent, reliable demonstration of this benefit could save thousands of lives each year

Even if longer-term tamoxifen is somewhat more effective than just a few years of treatment, the net advantage is likely to be only moderate. For example, five additional years of treatment would be unlikely to improve the 10-year survival by more than a few percent, and might not improve it at all. Indeed, if longer treatment produces extra side-effects, and little extra benefit, it might even make the 10-year survival slightly worse. Breast cancer is so common that reliable demonstration of just a small benefit or just a small hazard could save thousands of lives worldwide — and even a null result in a study big enough to be reliable would avoid the unnecessarily prolonged treatment of many hundreds of thousands of women each year.

Need for a large, pragmatic study of longer versus shorter adjuvant tamoxifen therapy

Around the world there are about a million breast cancer patients who are currently taking tamoxifen as an "adjuvant" treatment. These women could become candidates for the **Atlas** study at any time that they and their doctors become **substantially uncertain** whether to carry on taking the drug. Women who have received any type of curative surgery are eligible (irrespective of the original histological type of the disease, nodal status, or whether the tumour was estrogen receptor positive or negative) so long as the woman appears currently to be free from disease **and** is receiving tamoxifen **and** where both the woman and her doctor are uncertain whether to continue. Any other adjuvant treatments (eg chemotherapy, radiotherapy, ovarian ablation) may have been given. This pragmatic approach, by increasing the heterogeneity of the patient population, will enhance the medical value of the trial and make it easier for clinicians to enter their patients into the study. Women will be randomised **EITHER** to stop tamoxifen **OR** to continue tamoxifen for at least 5 extra years. To encourage wide participation, the **Atlas** study involves virtually no extra work for collaborators, so that even the busiest clinicians can take part. The entry procedure is quick and easy, no examinations are required beyond those given as part of routine care, and minimal, annual follow-up information is requested.

If **Atlas** includes many thousands of women then survival differences of just a few percent could be assessed reliably. The success of the study will therefore depend entirely on the extent to which clinicians invite their patients to join it. So, publication of the final results will be in the names of the many collaborators (not the central organisers), and the chief acknowledgement will be to the patients themselves.

The aim of Atlas is to assess reliably the balance of risks and benefits in prolonging the duration of adjuvant tamoxifen by at least 5 extra years.

INTERNATIONAL Version May 1997

ATLAS/P/2/497

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Contents

1. Background: a few years, or several years, of tamoxifen?

The first generation of trials of adjuvant tamoxifen in women with early breast cancer compared tamoxifen versus no tamoxifen, and most involved only 1 year, 2 years or 5 years of treatment. These early trials randomised a total of over 30,000 women, half of whom were allocated tamoxifen and half not. A systematic overview of the results[1] has shown a small but highly significant improvement in 10-year survival (overall about 6% absolute difference), with a tendency for the greatest improvement to be seen in the trials that studied the longest tamoxifen durations.

The second generation of adjuvant tamoxifen trials gave all patients tamoxifen, and involved directly randomised comparisons of different durations of tamoxifen with each other. Few of these trials involved more than 5 years of treatment, but again there was a tendency, within this range of durations, for the patients allocated longer treatment to have slightly better 10-year survival.

When really long-term follow-up becomes available from these first two generations of adjuvant tamoxifen trials, it will be possible to compare reasonably reliably the long-term effects of 1, 2 or 5 years of tamoxifen. By about 1990[1-4], however, the longer duration treatment regimens appeared somewhat more promising. Hence, many doctors began to recommend that adjuvant tamoxifen should continue for at least a few years, and, by the mid-1990s, about a million women worldwide were receiving the drug. There remained, however, wide uncertainty as to how long treatment should continue: is a few years generally sufficient, or would it be better to continue for several years (or even indefinitely)?

The first two generations of trials cannot answer this directly, as they do not provide reliable evidence about the additional effects of continuing beyond 5 years of treatment. Nor are there theoretical arguments that can resolve the question satisfactorily. As an anti-oestrogen, tamoxifen has a cytostatic effect, and it might be that maintenance of such an effect for several years would provide better disease control[5]. Conversely, it might be that virtually all of the protective effect against the original breast cancer could be achieved by just a few years of treatment, if this provided enough time without rapid cell growth for any clones that could be controlled by tamoxifen to become nonviable.

Moreover, while in the short term tamoxifen has few serious side-effects (especially among post-menopausal women), in the long term it can occasionally cause serious problems. In particular, the incidence of endometrial cancer is increased by tamoxifen[6-8]. It has also been suggested that the risk of liver tumours may be increased since hepatomas develop in rats (but not mice) who are regularly given large doses of the drug[9,10], although no clear excess of human liver cancer has been reported in the tamoxifen trials. Such tumours might, however, be mistaken for metastases in breast cancer patients[11]. During the first few years of adjuvant treatment the increase in endometrial cancer is outweighed by the decrease in breast cancer recurrence. But, any risks of tamoxifen-induced cancer may increase considerably if the drug is taken for many years, and this could alter the balance of benefits and risks against tamoxifen. There have also

been reports from non-randomised studies of tamoxifen-induced retinopathy[12] and depression[13]. Another putative side-effect of tamoxifen is thromboembolism. However, this may be counterbalanced by a reduction in coronary heart disease[14] with prolonged tamoxifen (perhaps due to its cholesterol-lowering effect[15]).

Some of the hypothesised risks of tamoxifen are speculative and some of the established risks are small, but they do indicate the need to evaluate the balance between any benefits and any risks particularly carefully, since long-term use of this drug could be envisaged for hundreds of thousands of women with a past history of breast cancer[16], many of whom may be entirely free of residual disease.

Hence, a third generation of trials is now needed, comparing what appear to be the best of the tamoxifen schedules already widely studied versus substantially longer treatment. By the mid-1990s, however, only about 1000 women have been randomised into trials of 5 years versus longer tamoxifen, whereas tens of thousands may need to be studied if appropriately reliable evidence is to emerge. **The Atlas study aims to contribute substantially to the provision of such evidence.**

2. Atlas Study Design

Large, simple study: minimal data collection and no extra investigations

The Atlas collaboration aims to randomise many thousands of women between stopping tamoxifen after some years of treatment versus continuing for at least 5 extra years. To make large-scale recruitment feasible, the Atlas study procedures are "streamlined" so as to impose almost no extra workload on participating clinicians, beyond that required to treat their patients. Entry can, depending on what is most convenient for particular doctors, be by post, by fax, or by a brief telephone call. The entry procedure ends with the patient's doctor being told (by return of post, return of fax or continuation of the same telephone call) whether the random allocation is to stop tamoxifen now or to continue for at least 5 more years. Thereafter, only the minimum data needed to evaluate the effects of tamoxifen on recurrence and survival are collected. There is just a short annual follow-up form which asks for one line of readily available data on the current status of each randomised patient. This information will be supplemented, wherever possible, by the use of national mortality records to ensure long-term follow-up. Regular newsletters will keep participants informed of the study's progress, and of any problems that are encountered.

Can a large, simple study like this work?

The treatment of acute myocardial infarction provides an example of the successful use of such large, simple randomised trials. The ISIS (International Studies of Infarct Survival) collaborative group of over 1000 hospitals worldwide randomised more than 100,000 heart attack patients into their trials within just a few years by addressing important therapeutic questions, by adopting very simple protocols, by basing eligibility on uncertainty in both the doctor and the patient and by imposing virtually no extra work on participants. Because of the "streamlined" trial designs, doctors who were uncertain which treatments to use found it almost as easy to put their patients into an ISIS study as to choose the treatment arbitrarily outside ISIS. (Even the largest previous trials in myocardial infarction had each recruited fewer than one thousand patients, perhaps because of the considerable extra documentation and investigations that they required.) Because the ISIS trials were so large they produced clear results that had a substantial impact on clinical practice. For example, definite benefits of fibrinolytic treatment and of aspirin were found in the ISIS trials[17-18], and these treatments rapidly became standard throughout the world[19]. As a result of these and other "mega-trials", tens of thousands of unnecessary cardiac deaths are being avoided each year.

Randomise when SUBSTANTIALLY UNCERTAIN whether to stop or continue tamoxifen

There is considerable variability in the length of time that women with operable breast cancer are prescribed adjuvant tamoxifen. Some doctors normally plan to give tamoxifen for just 2 years, some for 5 years and others for life. Individual clinicians have different practices for different patients that depend on the patient's age, risk factors and on how well tamoxifen is tolerated. For example, some doctors use tamoxifen for longer if the original tumour was estrogen-receptor-positive (ER+) than if it was estrogen-receptor-negative (ER-), while other doctors use tamoxifen similarly in both circumstances. Moreover, as new evidence evolves, clinical practice changes. This heterogeneity of clinical opinion means that different doctors would consider different durations to be appropriate for any particular individual. Hence, it is not appropriate to design a rigid protocol for a tamoxifen duration trial — such as 2 years versus 5 years, or 5 years versus life. The Atlas study therefore adopts a pragmatic approach: randomisation will take place when the woman and her own doctor become **substantially uncertain** as to whether to stop or to continue tamoxifen[20]. Women may therefore be randomised after any duration of prior tamoxifen treatment, although the evidence from the previous trials suggests that they **should probably have already received at least two years tamoxifen.**

Who is eligible for randomisation?

Any woman could be eligible if she had breast cancer removed some time ago **(Note A)**, is still now apparently healthy **(Note B)** and is currently taking adjuvant tamoxifen — as long as the woman and her doctor are both **SUBSTANTIALLY UNCERTAIN (Note C)** whether to stop tamoxifen now, or to continue for some years more.

Note A: Initial treatment. The original cancer may have been of any size or histological type (as long as the doctor now responsible for the patient considers it to have been a carcinoma of the breast), and may have been managed initially by any type of surgery and/or radiotherapy and/or systemic therapy (as long as some tamoxifen was eventually included in the initial treatment, and the doctor considers that no clinically detectable deposits of the disease now remain: **there are, however, no mandatory tests for this stipulated by the Atlas protocol**).

Note B: Still apparently healthy. An earlier history of local recurrence would not preclude randomisation into Atlas, again as long as the doctor considers that no clinically detectable deposits remain. No other seriously life-threatening diseases should exist.

Note C: Substantial uncertainty. The patient is eligible if there are not thought to be clear indications or definite contraindications to further tamoxifen — and, therefore, substantial uncertainty exists as to whether to stop or to continue tamoxifen treatment. Definite contraindications 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 anticoagulant 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, likely to move away)

Patient Information and Consent Leaflet

The patient should be told about the trial conversationally by her doctor and should be given time to read the detailed Patient Information and Consent Leaflet **(Appendix 1)**. She may wish to take the leaflet away to consider before deciding whether or not to join. If she decides to join the trial, she should be invited to initial each page of the leaflet and sign a formal statement of informed consent. The main source of information about the study should, however, be the patient's own doctor: the information leaflet is a medico-legal requirement, but it is of paramount importance that the woman understands the key reasons for and implications of the trial, which are as follows:

Entering the study: The woman's own doctor is substantially uncertain whether to stop tamoxifen now or whether to continue it for a few more years. This implies that the real advantages and disadvantages to be expected from either decision are probably quite small. If the woman also feels substantially uncertain whether to stop now or to continue taking tamoxifen for at least a few more years, then she may be willing to join the Atlas study and let the decision be taken just by the play of chance.

Withdrawing from the study: Because it is so difficult to measure small advantages or small disadvantages, the Atlas study is going to invite many thousands of women in hundreds of hospitals worldwide to join in, so it will not matter very much if a few of those who originally agree to join the study later change their minds and withdraw from it. If, after agreeing to join, a woman later changes her mind, then she is free to do so without needing to give any reason and without adversely affecting other aspects of her medical care. Similarly, the woman's doctor is free to give any other treatment or to change the duration of tamoxifen, if that is considered to be definitely in the patient's best interest.

Heterogeneous patient population required

Women who have received any type of "curative" surgery are eligible — irrespective of whether they had node-positive or node-negative disease, or ER+ or ER- tumours — as long as they seem to be currently free of disease, are currently receiving tamoxifen, and are unsure whether to continue. Any other adjuvant treatments (e.g. chemotherapy, ovarian ablation, radiotherapy), or none, may have been given. Basing eligibility on uncertainty should ensure large scale recruitment of an appropriately heterogeneous group. Heterogeneity of the types of patients randomised increases the medical value of the study, as it may make it possible to determine whether the net effects of tamoxifen are influenced by certain patient characteristics (e.g. high/low-risk, ER+/ER-, pre/post-menopausal) recorded at entry.

Other trials of tamoxifen duration

The Atlas collaboration is designed to supplement the results of other trials of tamoxifen duration, and is not intended to compete with them for patients. However, because of its wide entry criteria, Atlas could run in parallel with other such trials, randomising those patients for whom there is no appropriate other trial of tamoxifen duration for which they are eligible.

Patients already in other trials can be randomised into Atlas

Breast cancer trials that are not of tamoxifen duration may well be compatible with Atlas, as long as some or all of the patients in those trials are being given adjuvant tamoxifen. Hence, collaborative groups that are conducting such trials may wish to consider certain patients for joint entry, first into their existing trial and then, later, into Atlas (or may wish to append an Atlas-like randomisation as part of their own trial, conducting this independently of Atlas: this would be equally valuable).

3. Practical procedures

Listing patients on tamoxifen who may later become suitable for Atlas

You may wish, every year or two, to provide a list of all the women at your clinic who are currently taking adjuvant tamoxifen, and who might eventually become candidates for Atlas. A Future Atlas Patients Form, which may be used to compile such a list is provided in the Atlas Trial materials binder. A reminder can then be automatically sent to you on the date you have indicated that you intend to review the patient's need for further tamoxifen. At this time you can then consider inviting the patient to join Atlas .

Patients who are not yet uncertain

Women become eligible to enter the Atlas study once they and their doctor have become substantially uncertain as to whether to continue tamoxifen. Each time you review a patient who is receiving adjuvant tamoxifen, consider whether you are still reasonably certain that you wish to continue with such treatment. If you and your patient have become substantially uncertain as to whether or not she should continue tamoxifen, then she can be offered the opportunity to take part in the Atlas study. The Patient Information and Consent Leaflet **(Appendix 1)** should be considered by the patient before she decides whether to join the study. Some patients may wish to delay their decision for some days, months or years, and may wish to take away a copy of the information leaflet to help them think things over.

Randomisation by post, fax or telephone

At randomisation, you will be asked to provide patient identifying details and to give details of potentially important patient characteristics and previous treatments. Before randomisation, you should write in answers to ALL the questions on the single-sided Patient Entry Form **(Appendix 2)**. No special tests have to be carried out for a patient to be entered into Atlas and all the necessary information is provided by the Patient Entry Form. A unique patient code number and the randomisation are then obtained by post, fax or telephone:

either: post (using the FREEPOST envelopes [if available]) or fax (+44-1865-726003) the top copy of the Patient Entry Form (completed except for the treatment allocation) to the Atlas Trial Office for the random treatment allocation to be sent back to you **within a few days**

or: telephone +44-1865-240972 (24-hour service) or, where available, the national toll-free number which will be allocated by the Atlas Trial Office, and read out all answers (except ID box) to be given the random treatment allocation **immediately** as to whether tamoxifen should stop now or be continued. The top copy of the Patient Entry Form should then be posted or faxed to the randomisation service with the allocation written in.

The details for obtaining the randomly selected treatment allocation may vary between countries. The telephone and fax numbers and the postal address of the randomisation service given on the Patient Entry Form and on the back of the Protocol will be modified appropriately for each country. Each participating hospital is allocated an Atlas number which is on the Atlas binder and on the back of the pad of Patient Entry Forms. Giving this number at randomisation will speed up the randomisation.

Treatment strategies: continue tamoxifen, or stop now

Women allocated to continue tamoxifen should expect to carry on taking tamoxifen (preferably at a dose of about 20 mg/day, unless you prefer some other dose) for at least 5 more years unless a clear contraindication is thought by their doctor to have arisen. Tamoxifen should be continued at the same dose. In general, it is expected that the tamoxifen should continue to be paid for as before. In some countries this will mean that the patient is responsible for the cost of the drugs, whereas in other countries the cost will be met by the local health service or health insurance (in the same way as other such health costs). It is possible that in some countries, free tamoxifen provided by the pharmaceutical industry will be available and the details of its

distribution will be negotiated by the Atlas Trial Office in Oxford and separate National Coordinators. Women allocated to stop tamoxifen should stop tamoxifen as soon as conveniently possible, and should then continue to avoid tamoxifen unless a definite indication is thought by the patient's own doctor to have arisen.

Serious and unexpected adverse events

Tamoxifen is well-tolerated and only infrequently causes side-effects which are severe enough to require discontinuation of therapy. However, there is not enough experience of very long-term use of the drug to have definite evidence of the additional risks and benefits. The expected minor side-effects associated with tamoxifen do not need to be notified to the Atlas Trial Office and, as women in this study will have already received tamoxifen for some time, they will know whether any of these side-effects are relevant to them. Any serious and unexpected adverse events, believed to be attributable to tamoxifen, should be reported by the local coordinator to the Atlas Trial Office. **Serious** adverse events are those which 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 datasheet. If a patient becomes pregnant, tamoxifen therapy **must** be stopped immediately and the Atlas Trial Office informed. In addition, as part of routine practice, clinicians would still be 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.

Minimal data collection and no extra investigations

To produce medically reliable answers about long-term survival, Atlas needs to be very large, recruiting approximately 20, 000 women. But, in addition, Atlas is intended to be "streamlined", involving virtually no extra work for the clinician. To make it practicable for clinicians to participate, the collection of extensive data has been avoided. The current status of all patients will be ascertained through an annual follow-up listing that is sent out by the Atlas Trial Office at the same time each year, which requests only one line of data per patient **(Appendix 3)**. The information routinely recorded in the patient's records should be sufficient for the completion of the Annual Follow-up Form. Long-term mortality follow-up can, in some countries, be supplemented by central government records.

Investigations and management of patients differ at different centres and it is not appropriate to impose from outside rigid patient management procedures or extra investigations that would not be considered "best practice" by the patient's own doctor. Atlas therefore adopts a pragmatic approach with clinical responsibility for all aspects of the management of the patient always entirely remaining with the patient's own doctor. **In general, patients should not need to undergo any tests or examinations especially for the study.**

Details of the general organisation of the study are summarised on the inside of the back cover of the protocol. These may need to be modified for each country and the details will be negotiated by the Atlas Trial Office with the National Coordinators.

4. Analysis

Principal comparisons

The principal analysis will be of all-cause mortality (analysed by the logrank method on all randomised patients). This overall survival analysis will be complemented by subsidiary analyses of deaths from specific causes, such as breast cancer, myocardial infarction, endometrial cancer, etc. The incidence of second primary tumours — in particular, contralateral breast cancer, other female cancers and liver cancer — and of non-fatal myocardial infarctions and other vascular events requiring hospitalization will also be examined. The analyses will be stratified by the duration of tamoxifen given prior to randomisation (0-1yr, 2-3yrs, 4-5yrs,6-7yrs, 8-9 yrs, 10+ yrs), by age (<40, 40-49, 50-59, 60-69, 70-79, 80+), by ER status (ER-, unknown, ER+[i.e. ≥10fmol/mg of cytosol protein]), and by other prognostic factors recorded at randomisation.

Number of patients needed

Tamoxifen is generally well-tolerated, so it would be worth knowing if longer use of tamoxifen produced a difference in 10-year survival that was as small as just 2-3% or so. (By comparison, the difference in 10-year survival between those allocated about 2 years of tamoxifen and those allocated no tamoxifen was about 6%.) In order to detect such a small difference in absolute survival (e.g. 50% vs 52.5%), 20,000 patients would have to be randomised in this and other studies of tamoxifen duration for there to be a 95% chance of detecting a 2-3% difference in survival at $2P < 0.05$, and an 85% chance of doing so at $2P < 0.01$. (This number of randomised women would probably fail to detect a difference of only 1%, but would be virtually certain to detect a difference of 3% or more.) This number is considerably larger than any previous cancer study, but it is not disproportionately large if, during the years after the study ends, long term tamoxifen is prescribed without further controlled evaluation to many hundreds of thousands of women worldwide.

Data monitoring committee: determining when clear answers have emerged

If the survival benefit of longer tamoxifen is substantially greater than 2%, or if substantial side-effects emerge, then this may become apparent well before 20,000 patients are randomised into this and the other such trials.

During the period of intake to the study, interim analyses of mortality (and of any other information on major endpoints that is available) will be supplied, in strict confidence, to an independent data monitoring committee along with any other analyses that the committee may request. Reports of serious and unexpected adverse events attributed to tamoxifen will also be made available. The data monitoring committee will advise the chair of the steering committee if, in their view, the randomised comparisons in Atlas have provided both (a) "proof beyond reasonable doubt"* that for all, or for some, types of patient one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in long-term survival, and (b) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the other main study results. The steering committee can then decide whether to modify intake to the study. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the national or international clinical coordinators are unable to resolve any particular concern satisfactorily, collaborators and all others associated with the study may write through the Atlas coordinating office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

5. Financial support

Tamoxifen is already out of patent in many countries, and is likely to be out of patent in all countries before the main results emerge from Atlas. Trials of such non-patent treatments are important to patients, but can become large enough to provide reliable information only if doctors will collaborate in them without payment (except for recompense of any minor local costs that may arise). The central organisational costs and meetings costs of the trial are supported by the breast cancer program of the United States Army (log no. B4339128) and the UK Imperial Cancer Research Fund. Zeneca Pharmaceuticals plc have agreed to provide free tamoxifen in the trial, but the design and management of the trial remain entirely independent of the pharmaceutical company involvement. The company has no representative on the Trial Steering Committee to ensure that no suggestions of lack of objectivity of the findings can be justified.

6. Publication

The success of Atlas depends entirely on the commitment and efforts of a large number of collaborating doctors, nurses and patients. A meeting of the collaborators will be held at the end of the study to present and discuss the main results and the main results will then be published in the names of the professional staff who have collaborated in the study (not just the trial organisers), with the chief acknowledgement to the women who have participated.

Appendix 1: PATIENT INFORMATION AND CONSENT LEAFLET

INFORMATION AND CONSENT LEAFLET

Invitation to join an international research study of the efficacy and safety of prolonged tamoxifen treatment for women with a history of breast cancer

- You have been taking tamoxifen for some time, and your doctor is **uncertain** whether you should keep on taking it for a few more years, or whether you should now stop.
- If you too are unsure whether to continue or to stop tamoxifen now, then please consider taking part in a big research study involving thousands of women like you in hundreds of hospitals all around the world.
- If, on the other hand, you would definitely prefer to keep on taking tamoxifen, then ask your doctor to arrange this. Or, if you definitely feel that you have been taking tamoxifen for long enough already and would prefer to stop, then you should do so.

In the study, half stop and half continue tamoxifen

- The women who join the study will, like you, have been breast cancer patients who have been carrying on taking tamoxifen even though their doctors can no longer see any cancer anywhere.
- Half of them will be asked to continue taking tamoxifen for at least another five years

  (unless, later on, new evidence or some reason emerges why they should stop),

  and the other half will be asked to stop tamoxifen now and to stay off it

  (unless, later on, new evidence or some reason emerges why they should restart).
- If you decide to take part in the research study, neither you nor your doctor will know beforehand whether you yourself would be asked to continue or stop tamoxifen: that would be determined at random, just **after** you make a decision to take part.

You may wish to take a copy of this leaflet away to read before deciding whether to take part in the study.

If you eventually decide to take part, please initial and date each page and sign the back of this information leaflet.

Patient initials: _____ Witness initials: _____ Date: _____

What is the study about?

We know from previous studies of many thousands of women with breast cancer that taking tamoxifen each day, for at least the first few years after surgery, reduces the risk of the breast cancer returning. Tamoxifen does this by interfering with the effect of the natural female hormones on the growth of any traces of breast cancer that may have remained. What is not known, though, is exactly how long women should carry on taking tamoxifen. Because of this, there is currently a wide variation in practice, with some doctors prescribing tamoxifen for just one or two years, others for five years, and some for even longer. This is why we are doing this study, called **Atlas**, to help find out reliably which treatment duration is best.

What are the risks of carrying on taking tamoxifen?

Over a million women around the world have already taken tamoxifen for breast cancer and, so far, a few years of tamoxifen treatment has saved many lives and caused few serious side-effects. However, there is not yet enough experience with this drug to be sure about the additional risks and benefits of taking tamoxifen for a lot longer. In particular, we know that there is a small risk that tamoxifen will cause cancer of the lining of the womb (endometrium) — which, if caught early, can be successfully treated by hysterectomy. We also know, though, that a few years of tamoxifen has, so far, prevented many more breast cancers coming back than the few womb cancers it has caused. Eye problems have also been reported with tamoxifen and a rare complication, known as "tamoxifen retinopathy" can cause visual impairment (which usually disappears when treatment is stopped).

It has also been suggested that tamoxifen might have other side-effects: for example, prolonged high doses of tamoxifen produced liver tumours in some types of small laboratory animals (but not in others), although at present there is no good evidence of any increased risk of liver cancer in humans. Tamoxifen might also increase the risk of an internal blood clot (thromboembolism), but this may well be counterbalanced by a reduction in the risk of having a heart attack because of the cholesterol-lowering effect of tamoxifen. Some women taking tamoxifen report depression but, again, it is unclear whether or not this is caused by the tamoxifen. Less serious side-effects, which are usually mild and disappear when treatment has stopped, are reported by some women. These include changes in the pattern of menstrual "periods", hair loss, stomach upsets, itching, fluid retention, skin rashes and, in about 15% of women who are still having their periods (or who only recently stopped doing so), hot flashes. Since you have been taking tamoxifen for some time, you may well know whether any of these side-effects are relevant to you.

Extra years of tamoxifen

We very much hope that taking tamoxifen for longer than a few years will produce enough extra benefit to outweigh any side-effects. But, if the risk of womb cancer — or of any other serious diseases — increases when tamoxifen is taken for longer (or if tamoxifen becomes less effective at preventing the reappearance of breast cancer the longer it is taken) then it may be best not to go on taking it indefinitely. It is, therefore, important to know how long women should carry on taking tamoxifen. To find out the answer, we and many other doctors around the world are inviting women like yourself — for whom it is not clear whether it would be best to stop or to continue tamoxifen — to participate in a study comparing these two options.

Patient initials: _____

PATIENT INFORMATION AND CONSENT LEAFLET (continued)

What would the study involve?

If you are willing to help future women with breast cancer by taking part in Atlas, the only thing that you will be asked to do is **EITHER** to stop taking your tamoxifen tablets now **OR** to carry on taking them for at least another five years. If you are asked to continue taking tamoxifen then the costs of this treatment will have to be paid for in the same way as they have been up to now. If you agree to participate, the decision as to whether you will be asked to stop or to continue with tamoxifen would be made at random, by the central office running the study. This is the only way to find out really reliably which is the best treatment option. If subsequently, after joining the study, you later change your mind, then you are free to do so without needing to give any reason and without adversely affecting other aspects of your care. No extra tests or clinic visits would be needed if you took part in the study. Your doctor will, of course, continue to see you at routine intervals whether or not you take part.

What precautions should women on tamoxifen take?

You have already been taking tamoxifen for some time and so you will be aware of how it makes you feel, and of the precautions you should take and would have to keep taking if you were asked to continue with tamoxifen. In particular, because of the possibility that tamoxifen may affect the unborn child if taken by a pregnant woman, you should not enter the study if you think that you might be, or might become, pregnant. Women who are still fertile should take some reliable contraceptive measure if they are asked to continue tamoxifen and, if they do become pregnant while using tamoxifen, should immediately stop taking the tablets, tell their family doctor and contact the Atlas local coordinator (see below). If you already have a young baby then you should avoid breast-feeding while on tamoxifen. In addition, any unusual vaginal bleeding (which could be a sign of womb cancer but could also be due to a number of other causes), or any unusual problems with eyesight, or other unpleasant or severe side-effects, should also be reported without delay. If you do agree to take part, and you experience any ill effects because of doing so, you will receive all appropriate medical care, but there is no special compensation available to women for participation in this study — although you would, of course, retain your usual legal rights.

Confidentiality of patient details

If you do take part in Atlas, simple information about your progress would be provided each year, in confidence, by your own doctor to the central organisers. In addition, because the study receives funding from the Breast Cancer Program of the United States Army, the records of the research may be inspected by them as part of their legal obligations. The central organisers will have to send them the name, address and dates of participation of all of the women who agree to join the study. This information is to be stored for 75 years in case there are questions about someone's participation in research funded by the US Army, and to ensure that research volunteers can be adequately warned of any important new results that become available. This information, like all of the other information that is collected as part of the Atlas study, will be treated **in strict confidence** by the coordinating centre and all other investigators, in the same way as your other medical records. Neither you nor other patients in the study would be identified when the results are reported.

The protocol has been approved by the independent data monitoring committee, chaired by Professor Sir Richard Doll who can be contacted via the clinical coordinator Dr Christina Davies, Atlas Coordinating Centre, Radcliffe Infirmary, Oxford, England.

Witness initials: _____ Date: _____

Signed agreement to participate in the Atlas study

Having read this leaflet we hope that you will choose to take part in Atlas. If so, we need to ask you (and a witness) to sign below to confirm that you have agreed to do so, and you should both also initial and date each previous page to show you've read them. If you want further information about the study before deciding whether to join, then please feel free to ask the doctor who gave you the leaflet or the Atlas Local Coordinator (see below). If you want to delay your decision for a time, perhaps to discuss matters further, then please make an appointment to come back later. If you would like to ask anything about your rights while in the study, you can write to the chairman of the study's independent data monitoring committee (see previous page). If you decide not to take part, then you could choose to stop or continue tamoxifen as you wish in consultation with your medical adviser. If you do decide to join the study and then sometime later find there is some aspect of it that you wish to discuss further, then please contact the doctor who gave you this leaflet or the Atlas Local Coordinator (name and telephone number below).

I have been informed about the Atlas study and agree to enter it. I hope to collaborate in this study for several years, but I understand that I am free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care I can expect from my own doctors). I agree that simple information about my progress will be provided each year, in confidence, by my doctor to the central organisers and will be used for medical research only.

PATIENT SIGNATURE _____

& name (please PRINT) _____

WITNESS SIGNATURE _____

& name (please PRINT) _____

ATLAS LOCAL COORDINATOR:

STICK LABEL HERE

Appendix 2: ATLAS Study Patient Entry Form

ADJUVANT TAMOXIFEN — LONGER AGAINST SHORTER

PATIENT ENTRY FORM

After the patient has signed her consent, write in answers to ALL questions on this form, then:

Either: telephone the **Randomisation Service** and read out **all** answers (except ID box) for an **immediate** random treatment allocation (then post top copy to the Atlas Trial Office with allocation written in).

Or: post or fax top copy to **Atlas Trial Office** for random treatment allocation to be sent back to you **within a few days**

Date: ☐☐ day ☐☐ month ☐☐ year

ELIGIBILITY

Has the patient consent form been signed and witnessed?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Is the patient currently on tamoxifen?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Is the patient clinically free of cancer now?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Atlas code no. for hospital ☐☐☐☐
(see back of this pad, or front of binder)

If not known, give hospital name, city and country:

Name of hospital doctor responsible for patient (PRINT):

Patient's family name (PRINT):

Patient's given name(s) (PRINT):

Patient's hospital no. (if available):

Patient's date of birth: ☐☐ day ☐☐ month ☐☐ year

ID BOX — DETAILS TO BE WRITTEN IN, BUT NOT GIVEN OVER THE TELEPHONE

National ID/Social Security No. (if available)

Patient's address: (PRINT)

telephone:

ALTERNATIVE CONTACT

N.B. This person will be contacted only if contact with patient is lost.
(Choose someone at DIFFERENT address, e.g. family doctor/friend/relative) specify which:

Name: (PRINT)

Address: (PRINT)

telephone:

HISTORY OF CANCER

Date of diagnosis of original breast cancer: ☐☐ month ☐☐ year

Approximate diameter of primary tumour: ☐☐ cm ☐ Unknown

Any **ESTROGEN RECEPTORS** on primary? ☐ Negative ☐ Positive ☐ Unknown Exact value if known: ☐☐ fmol/mg

	NO	YES	Unknown	(Please tick ✓)
Loco-regional nodes ever involved?	☐	☐	☐	Exact count if known ☐☐/☐☐ (+/total)
Ever any loco-regional recurrence?	☐	☐	☐	If **YES**, Date: ☐☐ month ☐☐ year
Entire breast EVER removed?	☐	☐	☐	If **YES**, Date: ☐☐ month ☐☐ year
Ever any **CONTRALATERAL** primary, at diagnosis or later?	☐	☐	☐	If **YES**, Date: ☐☐ month ☐☐ year
Ever any other **PRIMARY** cancer, at ANY age?	☐	☐	☐	If **YES**, Date: ☐☐ month ☐☐ year

If **YES**, specify primary site(s):

PRESENT CIRCUMSTANCES

	NO	YES	Unknown	(Please tick ✓)
Post-menopausal?	☐	☐	☐	(or perimenopausal)
Ever hysterectomy?	☐	☐	☐	
Ever bilateral ovarian ablation?	☐	☐	☐	

Current TOTAL daily tamoxifen dose: ☐☐ mg/day **(CANNOT be zero)**

Duration in months of tamoxifen to date: ☐☐☐ months

CHECK ALL ANSWERS (ONE per LINE) ARE COMPLETED, AS ANY MISSING WILL PREVENT OR DELAY RANDOMISATION

RANDOMISATION ALLOCATION (stop / continue): LEAVE BLANK UNTIL ALLOCATED BY ATLAS

☐ **STOP tamoxifen now, or** ☐ **CONTINUE for at least 5 more years**

Patient identification number allocated at randomisation: ☐☐☐☐☐☐☐

Send **TOP** (Blue) copy to Atlas Trial Office

& keep the **BOTTOM** (White) copy for your clinical records

ATLAS/SE/1/296

ATLAS FOLLOW-UP: OCTOBER 1996

Name of collaborating doctor responsible for patients:_____
Name of local coordinator:_____
Participating hospital:_____

Listed below are patients who have been entered into ATLAS at your hospital and who, as far as we know, are still alive.
Please 1) check that the details given below are correct and 2) fill in ALL available additional information **since last follow-up and/or since entering ATLAS.**

Name of patient Date of birth [*Hospital number*] Date of original diagnosis Date entered into ATLAS ID number (STOP/CONTINUE)	Date last seen:	On tamoxifen when last seen?	Date of first loco-regional recurrence:	Date of first distant recurrence:	Other primary cancer: Date of diagnosis and Site[2]	If patient has died: Date of death and Underlying cause of death[3]	Any events involving hospital admission (e.g. myocardial infarct, hysterectomy etc): Date of admission[4] and Diagnosis	Other comments (e.g. name of hospital doctor currently responsible for patient, if different from above)
	/ m year	☐ Yes ☐ No[1] Date stopped[1] / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	
	/ m year	☐ Yes ☐ No[1] Date stopped[1]: / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	
	/ m year	☐ Yes ☐ No[1] Date stopped[1] / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	

1 If patient was allocated to STOP tamoxifen in ATLAS, date stopped should = date entered into ATLAS. If patient was allocated to CONTINUE tamoxifen in ATLAS, state date when stopped tamoxifen.
2 Other primary cancer includes primary contralateral breast. If more than one primary site, please specify EACH site and date of diagnosis (use "other comments" section).
3 If died, state whether UNCONTROLLED cancer was present (if known).
4 If more than one hospital admission, use "other comments" section.

PLEASE RETURN THIS FORM PROMPTLY IN THE ENCLOSED FREEPOST ENVELOPE (if available) TO:
Atlas Trial Office (see protocol cover for address)

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ATLAS: An International Tamoxifen Duration Study

Breast cancer patients now on tamoxifen: **STOP** or **CONTINUE TAMOXIFEN** a few extra years?

- Breast cancer some time ago **(Note A)**
- Clinically free of cancer now **(Note B)**
- Currently on tamoxifen but woman and doctor both UNCERTAIN whether to STOP tamoxifen now or CONTINUE a few extra years **(Note C)**

- Discuss ATLAS using INFORMATION LEAFLET and invite CONSENT **(Note D)**

- NO extra tests
- Complete all of short ENTRY FORM PRIOR to randomisation
- TELEPHONE for IMMEDIATE randomisation to:

EITHER

STOP CURRENT TAMOXIFEN IMMEDIATELY
(restarting ONLY if a definite indication is thought to have emerged)

OR

PLAN TO CONTINUE TAMOXIFEN (Note E) FOR AT LEAST 5 EXTRA YEARS
(stopping ONLY if a definite contra-indication is thought to have emerged)

- **or** POST/FAX form for randomisation in a few days

- NO extra tests
- CONTINUE allocated treatment strategy
- Annual FOLLOW UP: only 1 line of information per woman

Note A: Original cancer may have been of any size /type and original treatment may have been of any type. Tamoxifen **must** have eventually been included and women should **probably** have received at least 2 years of tamoxifen.

Note B: Still eligible if previous local recurrence but **must** be clinically free of breast cancer now.

Note C: Patient is eligible if there are not thought to be clear indications for or definite contraindications to further tamoxifen. Contraindications **might** be:

- significant endometrial hyperplasia
- retinopathy
- intended/actual pregnancy/lactation
- need for anticoagulant therapy
- serious toxicity **OR** little chance of worthwhile benefit
- other major life-threatening disease
- negligible risk of breast cancer death
- low probability of compliance

Note D: The patient should initial and date each page of information leaflet and sign the formal consent section.

Note E: Tamoxifen should be prescribed as before

24-hour randomisation: +44-1865-240972

- also for URGENT medical queries or for reporting SERIOUS and UNEXPECTED adverse events

For randomisation in a few days, fax: +44-1865-726003
or post to Atlas Trial Office in FREEPOST envelope

ORGANISATION OF THE ATLAS TRIAL

Atlas is designed to provide reliable evidence on the optimal duration of tamoxifen treatment. To be reliable, the study needs to be very large. This is achieved by adopting a very simple design, with streamlined entry and follow-up procedures to enable the trial to be easily integrated into routine clinical practice, so that most doctors can participate.

The overall administration and coordination of the trial is the responsibility of the **Atlas Trial Office** in Oxford, UK. For each country, there is a **National Coordinator** and/or **Regional Coordinator(s)**. Each participating centre will also have a **Local Coordinator**.

HOW TO ENTER A CENTRE INTO ATLAS

1 Each centre should first designate one person as the Local Coordinator who will be responsible for coordinating clinical, pharmaceutical and administrative aspects of the trial at that centre.

2 The Local Coordinator must submit the full study protocol to the local ethics committee/institutional review board for approval. **No patient can be entered into Atlas until ethics approval has been obtained.** An information sheet to assist with ethics committee submission is available either from the National Coordinator or from the Atlas Trial Office.

3 Confirmation of approval by the ethics committee **must** be forwarded to the Atlas Trial Office in Oxford.

4 The Atlas Trial Office will then send the trial materials to the Local Coordinator. Any doctor at the centre can then enter eligible patients into the study.

HOW TO ENTER A PATIENT INTO ATLAS

1 Women will usually be identified at a routine follow-up clinic. When eligible patients have been identified, have read the Patient Information Leaflet and have given their written consent, the Patient Entry Form should be completed fully.

2 The responsible clinician may then obtain the random treatment allocation **EITHER** by telephoning the 24-hour randomisation service in Oxford (+44-1865-240972), or where available the national toll-free number for immediate randomisation, **OR** by sending the Patient Entry Form by fax (+44-1865-726003) or by FREEPOST (if available) for randomisation within a few days.

3 **If telephone randomisation is used:** the random treatment allocation and the patient identification number assigned by the randomisation service should be written on the Patient Entry Form. The top copy of the Patient Entry Form must then be sent by FREEPOST (if available) to the Atlas Trial Office.

4 **If fax or postal randomisation is used:** the random treatment allocation and the patient identification number will be assigned by the randomisation service and then returned to the clinician randomising that patient.

5 "ATLAS Patient" stickers are provided to identify the notes of patients who have been randomised on Atlas.

6 Some patients may definitely wish to continue on tamoxifen at the present time, but may become eligible for Atlas at some time in the future. To help identify these patients, "?ATLAS" stickers, which can be attached to the patients' notes are provided. In addition, a Future Atlas Patients Form can be used to list these patients, and to indicate when they might become eligible for the study. If it would be helpful, the Future Atlas Patients Form may be sent to the Atlas Trial Office, which will send a reminder notice to the responsible clinician at the appropriate time.

FOLLOW-UP OF PATIENTS IN ATLAS

The Atlas Trial Office is responsible, in collaboration with National Coordinators, for the collection of follow-up data. At the same time each year, the Atlas Trial Office will send out simple single sided Annual Follow-up Forms requesting simple information from each clinician on each patient entered into Atlas. This form should be completed and returned as soon as possible to the Atlas Trial Office using the FREEPOST envelope (if available).

HOW TO REPORT ADVERSE EVENTS

Clinicians or the Local Coordinator should telephone the 24-hour randomisation service (+44-1865-240972) if any patient who is receiving tamoxifen in Atlas becomes pregnant, or experiences serious and unexpected adverse events which are considered to be attributable to tamoxifen.

Serious events are those which are fatal, life-threatening, disabling and/or incapacitating, require hospitalisation, or are a congenital anomaly, a new cancer or an overdose. **Unexpected** events are those which do not appear in the current tamoxifen datasheet. In addition, as part of routine practice, clinicians would still be expected to follow their usual procedures for reporting adverse events.

HOW TO GET ADVICE

For **urgent** medical enquiries, call the 24-hour randomisation service (+44-1865-240972), or the National/Regional Coordinator.

For general and administrative enquiries, call the Atlas Trial Office (+44-1865-794569)

HOW TO GET STUDY SUPPLIES

For trial supplies (study protocols, Patient Entry Forms, Patient Information and Consent Leaflets etc.), call the Atlas Trial Office (+44-1865-794569) or the National/Regional Coordinator.

RESPONSIBILITIES OF LOCAL COORDINATORS

1 **Applying for local ethical approval for Atlas.** Any modifications, particularly to the Patient Information and Consent Leaflet, however minor, will need to be sent to the Atlas Trial Office for formal review and, as this will involve delay, any changes are discouraged.

2 **Maximising collaboration in their centre, by ensuring that local medical and nursing staff involved in the long-term care of breast cancer patients are informed about Atlas.** This may be through discussions and meetings. Atlas wall-charts can be displayed, and regular newsletters will be produced and distributed by the Atlas Trial Office.

3 **Maximising randomisation of eligible women into Atlas.**

4 **Answering patients' enquiries about the study.**

5 **Ensuring that the Atlas Trial Office is notified** if any patient who is receiving tamoxifen in Atlas becomes pregnant, or if any patient experiences serious and unexpected adverse events which are considered to be attributable to tamoxifen.

6 **Provision of tamoxifen.** In women allocated to the continuation of tamoxifen arm, tamoxifen should continue to be prescribed as before. In general, it is expected that tamoxifen should continue to be paid for as before. In some countries, this will mean that the patient is responsible for the cost of the drugs, whereas in other countries, the cost will be met by the local health service or health insurance (in the same way as other such health costs). In some countries, free tamoxifen provided by the manufacturers will be available. Details of its distribution will be negotiated by the Atlas Trial Office with the National/Regional Coordinators, who will in turn discuss needs with the Local Coordinators.

RESPONSIBILITIES OF NATIONAL/ REGIONAL COORDINATORS

1 **The National and/or Regional Coordinators are in regular and direct contact with the Atlas Trial Office,** and will be the main source of advice to participating clinicians in those countries about Atlas.

2 **Maximising collaboration in their region, and arranging occasional meetings of collaborators** so that any problems or questions can be dealt with.

3 **Distributing trial materials and newsletters, informing local collaborators about the progress of Atlas and dealing with most of the problems and questions that might arise.** This includes advising the Local Coordinators on the appropriate action to take if any patient on tamoxifen in Atlas might be pregnant or if any patient experiences serious and unexpected adverse events.

4 **Where necessary, coordinating free tamoxifen to participating centres.**

5 **Representing collaborators' views at meetings of the Atlas steering committee of which the National Coordinators would be members.**

GENERAL ORGANISATION OF THE ATLAS TRIAL*

Atlas Trial Office

- **Overall coordination and administration**
- **Production and supply of trial materials and newsletters**
- **Randomisation service**
- **Data analysis**

National and/or Regional Coordinators

- **Promoting collaboration in the region**
- **Advice to participating clinicians**
- **Liaising with the Atlas Trial Office**
- **Distributing trial materials**
- **Coordinating distribution of free tamoxifen (where necessary)**

Local Coordinators at centres

- **Promoting collaboration in the centre**
- **Obtaining local ethical approval for the study**
- **Notifying the Atlas Trial Office of serious and unexpected adverse events**
- **Answering patients' questions about the study**

Clinicians

- **Entering patients in the study**
- **Providing annual follow-up data**

* Details of the practical arrangements for implementing the trial may vary in different countries

[redacted]

From: Miller Virginia M [Virginia.Miller@DET.AMEDD.ARMY.MIL]
Sent: Wednesday, October 06, 1999 11:04 AM
To: [redacted]
Subject: ADA360842

~~Good morning Loretta,~~

Could you please correct another document in DTIC for us? The document, ADA360842, was forwarded to DTIC as a Final Report (for the period 1 Oct 94 - 31 Aug 98). Could you please change the type of report on the cover and 298 to: Annual Report and change the period of time on the 298 to: 1 Oct 97 - 30 Sep 98. The PI was given an extension in time to February 2000 and will be submitting another final report. Thank you so much for all your help.

Virginia

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