Experiences of a long-term randomized controlled prevention trial in a maiden environment: Estonian Postmenopausal Hormone Therapy trial [ISRCTN35338757].

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ABSTRACT

Few reports have described the process in long-term trials in practice. The purpose is to describe the research process of a long-term randomized controlled trial and discuss the impact of changes in the research environment. The Estonian Postmenopausal Hormone Therapy trial (EPHT) was established to study the effects of hormone therapy on chronic diseases and fractures, well-being, social effects, health service use, and the effect of blinding on recruitment and results. The data of this report on description of the process comes from written material such as notes and minutes from meetings, trial study recommendations and articles, letters, participatory observations, and two surveys: one given to 2000 women aged 45-64 in 1998, and another given to 500 physicians in 2000. New legislation and organizational changes during the trial period (1998 to 2004) demanded constant actions, but emerging technology made everyday management of the trial easier. Significant results from other hormone therapy trials compelled us to change the trial protocol, and the EPHT was stopped earlier than planned on the recommendation of the data monitoring committee. Reports detailing with these kinds of changes are useful to help future long-term trials to anticipate possible changes. [ISRCTN35338757]

Keywords: Estonia; Randomized controlled trials; Primary prevention; Postmenopausal hormone therapy; Replacement therapy, hormone; Postmenopause; Health services research
Introduction

Preventive medications and sometimes licensed drugs require long-term trials to show their effectiveness or side effects. A trial of long duration brings more demands to a study. Very few reports have described the long-term trial process in practice; it has remained something of a black box. When trial processes are not described publicly, useful knowledge fails to accumulate. Especially for trials that are unable to meet their targets, information about the process is important to aid other researchers in anticipating and avoiding similar problems.

Previous studies of the process of preventive trials have mainly concerned the recruitment process (1-4), failures in recruitment (5), the non-medical intervention effect on compliance (6, 7), and randomization (8). Oakley et al. (1, 9) have reported a trial process on social support in motherhood and on peer-led sex education. They found that an evaluation of the process was integral to understand the outcomes. In a trial on delivery of very low birth weight infants, Lumley et al. (8) failed to achieve randomization because of a critical shift in obstetric practice. In Finland the pilot for a non-blind, patient-managed trial on hormone therapy (HT) revealed several obstacles to a main trial, including the difficulty to discontinue HT and a negative attitude among Finnish physicians towards the trial (4).

We have found no process description of a successful trial involving preventive drug therapy. To run a trial over many years involves a significant likelihood that obstacles will emerge. The purpose of this article is to describe the research process in a long-term randomized controlled trial, the Estonian Postmenopausal Hormone Therapy trial (EPHT), and to discuss the impact and consequences of changes in the research environment.

The EPHT trial
The EPHT trial was to study the long-term health effects of HT on the risk of cancers, heart and cardiovascular diseases, fractures and metabolic diseases, the immediate effects on well-being and symptoms, effects on experiences of the climacteric and ageing, effects on partner relationships, health services use, and also the effect of blinding on recruitment and results.

Trial planning was started in 1995. The EPHT trial was a four-arm randomized controlled preventive trial on menopausal hormone therapy (HT), originally planned for five years exposure, consisting of a blind and a non-blind sub-study (Figure 1). The blind sub-study represents a traditional randomized, double-blind, placebo-controlled trial except for the early randomization prior to informed consent, whereas, the non-blind sub-study was a randomized controlled trial with an open-label HT arm and a non-treatment arm.

Participants were recruited in Estonia using a postal questionnaire to establish eligibility and to ask whether they wished to participate in the trial. Those positive and potentially eligible women were randomized to the four trial arms (HT and a placebo in the blind group, and open-label HT and no treatment in the non-blind group). Women were mailed a letter briefly describing either the blind or non-blind group to which they had been randomized and inviting them to the recruitment examination in one of the study clinics. (10). The EPHT trial had three study centers, two women's clinics in Tallinn, the capital of Estonia, and a university women's clinic in Tartu, southern Estonia. Trial staff in each study centre consisted of 2–3 gynecologists and two midwives in each clinic, 13 altogether.

Local coordination in Estonia was at the Institute of Experimental and Clinical Medicine (EKMI), which as of May 2003 became known as the National Institute for Health Development (TAI). In 1998 the trial received a positive statement from the Tallinn
Committee of Medical Ethics, and the trial was registered at the State Agency of Medicines in the same year.

The trial drug was licensed in the USA and was a combined regimen of conjugated equine oestrogens 0.625 mg (CEE) and medroxyprogesterone acetate 2.5 mg (MPA). A similar drug with a higher MPA dose (10 mg) had already been licensed in Estonia. The EPHT trial obtained the drugs from the pharmaceutical company Wyeth as a result of EPHT trial’s co-operation with the Women’s International Study of Long-Duration Oestrogen after Menopause (WISDOM).

In the mid-1990s, the UK-based WISDOM unsuccessfully sought financing from the European Union (EU) for a large European HT study (11). The UK Medical Research Council (MRC) decided to finance the trial covering UK, Australia, and New Zealand. In view of this decision, we planned our trial as an independent study, though still working closely with WISDOM. The disease outcomes of our trial were to be pooled with those of WISDOM.

Recruiting took place from January 1999 to December 2001. Women were to visit the study clinics semi-annually to collect their trial medication, and annually for an examination by the study physician; this did not apply to women in the no-treatment-arm in the non-blind group, who were to visit only if needed.

Financing for the trial came from public sources such as the Academy of Finland, STAKES, the Finnish Ministry of Education, and the Estonian Ministry of Education and Science, while the Universities of Tartu (Estonia) and Tampere (Finland) and the Estonian National Institute for Health Development (TAI, previously EKMI) offered institutional support.
Originally, the study was planned to be closely connected to a large UK-based study (WISDOM), but due to the premature closer of that study (see the results section), this was not realized.

**Sources of material**

The material was drawn from written documents and letters, participatory observations, and surveys. The written material included notes and minutes from EPHT meetings, trial guidelines with recommendations for clinical practitioners, articles, published trial research reports, and correspondence. Participatory observations were made during visits to the study clinics and in discussions with Estonian health professionals, international researchers, and the research team. In order to study women's and physicians' opinions on the climacteric and HT, two surveys were conducted: in 1998 a survey was sent to a random sample of 2000 women aged 45–64 (12) and in 2000 a survey was sent to a random sample of 500 gynecologists and family practitioners (referred to as general practitioners in this paper) in Estonia (13).

One of the trial researchers (SLH) has been involved with the trial since 1995 and worked as the coordinating trial investigator, beginning with the EPHT pilot study in 1997. SLH has systematically made notes and filed correspondence during the trial process. Piret Veerus (PV) has been involved in the trial in Estonia since 1997, first as a clinical expert, and since 2000 as the local coordinator in Estonia. Elina Hemminki was the principal investigator of the EPHT trial and Mati Rahu was the leader in Estonia.

**Impact of various factors on trial process**

6
1. Impact of other studies on EPHT

Recruiting occurred between 1999–2001 (Figure 2). Half a year after recruiting was completed (July 2002), the Women's Health Initiative (WHI) prematurely published its results in the USA. This had a big influence on our trial, both directly and through its impact on WISDOM. The WHI was initiated in 1992 with a planned completion date of 2007. It included two large trials to investigate the effects of HT on the morbidity and mortality of postmenopausal women aged 50 to 79. Between 1993 and 1998, the WHI randomized 16,608 women to the estrogen plus progestin trial (14) and 10,739 women without uterus to the estrogen only trial (15) to be treated for an average follow-up of 8.5 years (14). The drug in the first trial was the same as that used in our trial (combined CEE and MPA) (16).

In 2000 and 2001, the WHI Data and Safety Monitoring Board recommended that the participating women should be informed that the original hypothesis of cardiovascular protection was no longer likely, but that the trial would continue because the balance of risks and benefits remained uncertain. In July 2002, the WHI estrogen-progestin trial was stopped because the number of breast cancers found exceeded the predefined limits and the overall risks were seen to exceed the benefits as measured by the global disease index (14). By summer 2003, results in several articles emerging from the WHI trial showed that HT is not safe for disease prevention (14, 17-19). The trial with estrogen alone continued until early 2004 when the intervention was withdrawn because the original hypothesis of estrogen preventing the risk of cardiovascular diseases was unlikely (15).

After we became aware of the WHI warnings to its trial participants in 2000 and 2001, we kept ourselves updated via the WHI web site. We also tried to get further information with direct contacts, but were not successful. The original information given to our trial women
said that "HT probably decreases cardiovascular diseases (CVD), and estrogen is thought to have specific effects on blood coagulation and plasma lipid concentration, but their effect on CVD is still not clear. It is assumed that HT decreases the risk of myocardial infarction, but it may increase the risk of thrombosis for some women." Thus, we did not change the protocol in summer 2002.

By autumn 2002, WISDOM had recruited 5700 women. After WHI prematurely stopped its first trial in July 2002, WISDOM's Data Monitoring and Ethics Committee recommended WISDOM to continue as long as women were informed of the current state of knowledge. Likewise, the Trial Steering Committee recommended continuation as they found no strong scientific or ethical reasons to stop. However, the Medical Research Council (MRC), who were the main funding agency, decided to convene an Independent International Committee to review the WHI findings, the progress of WISDOM and other evidence. The Committee concluded that "WISDOM was unlikely to provide substantial evidence to influence clinical practice in the next 10 years" (11). MRC decided in October 2002 to stop the funding of WISDOM on the basis of the lack of importance (20).

The halting of WISDOM in October 2002 did not have an immediate effect on the continuation of our trial. In November 2002 the EPHT Data Monitoring Committee (DMC) made the annual interim analysis of the data and found no results that would have demanded cessation of the trial. A strong argument for us to continue the trial was the WISDOM steering committee's recommendation to continue WISDOM. An important reason behind the MRC decision to stop WISDOM was financial rather than safety concerns and we felt that many unanswered research questions favoured the continuation of our trial. However, as the WHI results suggested that breast cancer risk increased by the length of exposure, we decided to shorten the trial treatment to four years from the original five for those women
who had not yet been in the study for 4 years (December 2002). We also kept the trial physicians and midwives informed, while the participating women were kept up to date on the results of other trials with a semi-annual newsletter. Women were told why WHI was stopped, and were given the disease outcomes per 10 000 women for those using or not using HT. Women were told that they had been in the trial for a shorter period than women in the WHI, and women with less than four years of exposure were encouraged to continue the trial treatment. We encouraged the women to contact the researchers if they wanted more information.

In August 2003, following the release of the WHI results of HT effects on dementia, cognitive functions, and quality of life (17, 19, 21), and the results from the Million Women Study on HT effects on breast cancer (22), we shortened the exposure in our trial for a second time. The exposure was shortened to three years for women who had by that time received it for less than three years. In December 2003, our trial DMC recommended ceasing the trial treatment, as results from other trials were against the preventive use of HT. We stopped the treatment over a period up until May 31st 2004 to enable a final medical examination to all women. As a result, 597 women received trial treatment at least for four full years, 808 for three years, and the rest 418 at least for two years (Table 1).

Our trial received its drugs from Wyeth via WISDOM. After WISDOM was discontinued, to receive more drugs, we sent Wyeth an application for registration in their trial registry. However, the registration was never finalized: during the lengthy negotiations, we had twice shortened the trial, and in the end no more drugs were needed.

The new information coming out from other trials led to a lot of additional work: we had to thoroughly analyze the data and consider its impact on our study protocol, to inform both
women and the clinical staff, as well as to monitor news reports. In 2002 the results of the WHI estrogen/progestin trial were widely discussed both in the professional and lay-press (see e.g. (23)). However, in Estonia it did not raise any public discussion. We detected no peak in the numbers discontinuing our trial treatment, and only a few women had contacted the trial staff because of the new warnings. Following the summer of 2002, we did not try to actively improve the adherence to trial treatment, and we emphasized to the women the importance of the annual check-ups.

2. Impact of changes in the local health care system and legislative acts

Between the initial planning year (1995) and the halting of the intervention (2004), Estonian society changed very rapidly. Estonia had been a part of the Soviet Union with a planned economy up until 1991, when it became independent. Before 1991, medical technology, including medicines, came via Moscow. By 1994–95 pharmacies had been privatized and the availability of drugs was no longer a problem and pharmacotherapeutic choices were determined mostly by prescribers (24). In 2004 Estonia became a member of the European Union and its economic and scientific contacts with Western Europe increased. Independent Estonia had adopted a liberal market economy and income had increased, but less for poor people. The market economy also led to changes in health care financing (25).

In the early 1990s, Estonia was still a maiden country for conducting a trial with HT. HT use did increase in the 1990s, but by 2000 it was still notably lower than, for example, in Finland (26). In a survey in 1998, only 4% of women aged 45–64 reported current use of HT [compared to what in Finland?] (12).
Various changes in legislation, relevant institutions, and financing occurred during our trial. Our study clinics were financed by the Estonian Sickness Insurance Fund (later Health Insurance Fund). Changes in the administration of the Health Insurance Fund required us to conduct several negotiations to ensure continuation of the trial. In 1992 a restructuring saw 22 Health Funds established around the country. The number of local health insurance funds decreased in various steps between years 1995 and 2003 (from 15 to 4), strengthening centralized functions (27).

Reorganization also affected the participating research institute, the Institute of Experimental and Clinical Medicine (EKMI), which became the National Institute for Health Development (TAI) as of May 2003. Furthermore, during the trial period salaries rose about 30%, which tightened the trial budget, which had initially been planned in 1997.

While Estonia has good health registries, at the planning phase of the EPHT, Finland had better developed practices in data protection than Estonia and so these were adapted to our trial. During our trial, various changes were made to the Estonian data protection laws that led to reduced access to various registries. The 1996 Data Protection Law, or its updated 2003 version, were not clear in regard to the use of registries for research, (28) with the ambiguity in interpretations causing additional work and delays in obtaining outcome data. A rapid turnover of personnel in the ministries reduced experience in data protection practices. The trial participants had signed informed consent permitting their survey and health examination data to be linked with health registries, but the right to linkage was initially challenged by the data protection authority. Furthermore, maintaining up-to-date addresses for the participating women who had moved residence became difficult, because we were not allowed to check addresses from the population registry. Also, the Estonian Cancer Registry did not get mortality data for a period from 2000 to 2003 due to changes in
the Data Protection Law and the quality of the linkages with the database was much decreased.

Data collection for disease outcomes in our trial was mainly based on registries, and new and changing regulations meant extra negotiations and time delays. Nevertheless, all necessary data other than deaths had been obtained up to the end of 2004 as planned.

At the start of the recruitment in 1999, screening for breast cancer with mammography was not in use in Estonia, not even among HT users. If a woman had breast problems she was referred to a mammologist, a specialized physician. We advised our study women to regularly palpate their breasts through the Mama breast self-examination program (29). However, beginning in 2000, mammogram screening in Estonia was gradually introduced. This development—in addition to the advice given by local mammologists—led us to add mammogram screening for all trial women who had already been in the trial for two years (Figure 2). Those women who were eligible for local free–of-charge mammogram mass-screening programs were encouraged to use the service. For others the costs were covered by the trial, and they were unexpectedly high.

A number of positive developments during the trial period involved improved technology for communications and trial management: electronic mails replaced faxes, mobile phones made contacting individuals easier and travelling became notably faster. In the mid-1990s a journey from Helsinki to Tallinn (70 kilometres over sea) took about 3.5 hours with only two ships each operating once a day. The customs operated very slowly at between the EU country of Finland and Estonia, then not an EU member. A visa was necessary until the summer of 1997. Since 1997, fast boats have operated except in winter, and by 2002 were departing almost every hour, with a reduced journey time of 1.5 hours. Since 2000, a
helicopter service has also been available. With Estonia's full membership in the EU in 2004, passing through customs became quicker.

By the mid-1990s, prices and salaries in Estonia were lower than in most Western European countries, but the infrastructure (including health services) was good and western-style legislation and regulations had been developed (30). The Estonian Health Insurance Fund Database, the Estonian Cancer Registry and the Estonian Mortality Database made it possible to collect information about women's health and health services use. The Estonian Health Insurance Fund Database is unique and includes information on all health care visits, diagnosis and prescriptions (31). Many foreign drug companies were interested in Estonia and the number of approved clinical trials increased from five in 1992 to over 80 in 2004 (32). With the increasing number of trials, we had to ensure that the women participating in our study were not recruited to other trials.

3. Impact of using a licensed regimen

The estrogen used in our study (CEE) had been available since the 1940s (33) and combined estrogen-progestin since the 1970s (34). A wide variety of preparations have been available for climacteric women (35). When we started our trial, HT was already available and in use in Estonia, including the specific trial regimen.

Studying an established therapy had its advantages and disadvantages. An advantage is that the ethical burden is lessened because women outside the study can be freely prescribed the drug. A disadvantage is that compliance in the non-drug group can be easily compromised through purchase of the drug outside the study. This was not a major issue in our trial: only some women receiving the placebo and less than 10% in the no-therapy group had been subsequently prescribed HT by the exposure end (36).
The WHI researchers had chosen conjugated equine estrogens (CEE), which is the most widely prescribed preparation in the USA, but rarely used in Europe. WISDOM approached major HT manufacturers, but Wyeth was the only company prepared to supply drugs and matched placebos (11). So, both the WHI and WISDOM ended up studying the same type of HT out of the dozens of preparations available.

As a consequence, most health data now available in relation to long-term HT use are based on one type of drug and, for example, transdermal preparations remain untested over the long-term. Before the start of the WHI and WISDOM, the applicability of specific HT preparations or formulations was not questioned (11), but later proponents of preventive HT have used the specific features of CEE as one argument to support continued use (23).

4. Impact on the views of attitudes of participants and physicians

In Estonia most women were of the opinion that the climacteric is a normal phase in a woman’s life which does not need medical treatment (12). Few women were familiar with HT and most could not take a stand on its health benefits (12). Women's inexperience and hesitation in regard to HT may have contributed to the low adherence in the placebo and HT-groups in the trial (36). On the contrary, according to our survey in 2000, Estonian gynaecologists favoured HT and recommended HT for postmenopausal women in climacteric (13). GPs referred almost all of their patients with menopausal symptoms to a gynaecologist. Physicians thought that the increase in the use of HT in Estonia was more based on changes in physicians' opinions than that of women. Gynaecologists had frequently participated in education on HT, and education was often supported by industry (26). Trials can be considered as a means to increase drug use, and this possibly contributed to physicians supporting our trial.
In preparing the information leaflets for women, it was revealed that still in the 1990s many physicians had paternalistic behaviours and that it was not considered crucial to inform patients. Discussions about cancer risks still seemed to be a taboo (26).

5. Impact of public funding

The absence of a sponsoring drug company led to extra work. An application to the Estonian drug control authority for permission was unproblematic. However, the first shipment of drugs was in bulk and the Estonian law required that the tablets have to be packed into vials and labelled by a pharmaceutical company. Because of the small number of tablets packing would have to be done by hand, and many negotiations were needed before we reached an agreement with a local pharmaceutical company. However, the next shipment of drugs was actually pre-packed, with 215 tablets in each vial i.e. for seven months use. But we still needed a pharmaceutical company to put the labels on the vials. The company who had done the packing did not want to do it and we had to find a new company. More importantly, this changed the time of the second visit: the six-month visit was changed to seven months.

When we started our trial in Estonia, the culture of doing clinical trials was still new. Compared to the pharmaceutical companies, our resources were small, but due to the strong local academic participation, we had been successful in recruiting capable gynaecologists and midwives and had only a small turnover of research personnel. We organized semi-annual seminars for the clinical staff on research methodology and controlled trials. In addition, when the local research assistant visited the clinics to follow the recruitment process and collect weekly summary sheets, she also discussed the trial progress with the midwives, and offered help in the case of problems.
In the EPHT trial, all the trial clinics were located in Estonia, but the main scientific coordination was in Finland. Health care was different between the two countries. Personal contacts and open discussions were most valuable in bringing to light the different practices and in finding solutions. Many external changes placed additional demands especially on the local coordinator, who had to seek new solutions and contacts. The small degree of financial resources did not make things easier.

**Discussion – keys for success**

Treatment in the EPHT trial was stopped earlier than planned, but the time was sufficient to provide answers to our short-term research questions. Taking into account all the outside changes occurring during the trial, we are satisfied with the trial process. However, the low adherence and the relatively short exposure time reduced the power of the study. The relative success of the trial was due to a minimal clinical staff turnover and tireless negotiations with authorities. Repeated changes in the health care system and in legislation were keenly followed up by appropriate actions. Preventive drug trials usually have a long duration and the pressures for changes to the protocol are strong. Our trial was a small-scale trial which meant that it was easier to manage in the face of such constantly changing circumstances: the organizing was flexible, while participants both in the decision-making board and the clinics were fully committed to the trial.

Financing is a major challenge in a long-term preventive trial. During the trial some unexpected expenses occurred and prices increased much faster than could have been expected at the time of planning. Furthermore, in the Finnish financing system, funding decisions usually cover only a couple of years at a time, budgets are often made on current
prices and resources are bound to budget years. More flexibility and longer commitment in financing would help in administering a long-term trial.

In preventive drug trials the costs of drugs are usually high. Even publicly funded researchers usually ask for drugs to be donated from drug companies. Drug companies may not be so enthusiastic about sponsoring trials of an established therapy, because it is a financial risk. Beneficial results may increase sales, but not necessarily of the specific product of the sponsoring company. If the results are negative, pharmaceutical competitors may attempt to deflect the impact by insisting the negative results apply only to the drug used in the study.

In case of the WHI and WISDOM, Wyeth Ayerst was the only pharmaceutical company willing to take the risk. In 2001 Wyeth covered 70% of the global market (37). When the non-beneficial results from the WHI were released in June 2002 the sale of HT in the USA declined, with the decline in Wyeth products being especially dramatic (38-40). Those companies that did not take the risk of donating drugs for the trials could now argue that their regimens are different from Wyeth's and the trial results do not apply to their products.

An important question is who should prove the effectiveness of an (old) drug for new preventive indication. Preventive drug trials are often long-term, and usually need large numbers of participants, thus increasing the costs involved (16, 41). Preventive trials need to be carried out over an extended period because the main outcome measurements usually require long exposure or long follow-up to be detectable. Public funding is crucial in maintaining the independence of the trial from commercial biases.
HT, although used as a preventive medicine, is different from other preventive interventions—a vitamin trial for example—in respect to treatment effect. Often in long-term preventive drug trials, no immediate effects are noticed. Taking a vitamin does not show any obvious outward signs but taking an estrogen/progestin tablet may cause symptoms such as bleeding or breast tenderness, or relieve vasomotor symptoms. In our trial women mentioned side-effects as the most common reason for their discontinuation, and more often in the HT arms than in the placebo arm (36). Adherence in the EPHT trial was low, and resembled that found in ordinary use.

Having a constant contact with the study clinics was extremely important. Practices in the clinic changed and midwives held other clinical duties in addition to our trial. An experienced clinical eye can identify whether changes have been made to the study protocols that may impact on the trial results in ways unforeseen by the health staff.

A big threat to long-term trials is new information from other trials challenging the hypotheses and initial reasoning of the trial. In the case of WISDOM, a large-scale, well-prepared trial was terminated in an early phase. The wisdom of that decision can be questioned, especially in the light of the slow changes in the practice of HT use and the current criticism of a lack of information. However, there is very little to be made to this extraneous threat to long-term trials, besides reconsiderations of the norms used in terminating trials.

Acknowledgements. The trial was financially supported by The Academy of Finland (Grant number 69838 and 201490), STAKES, the Finnish Ministry of Education (Doctoral Programs in Public Health), and the Ministry of Education and Science in Estonia, and the National Institute for Health Development in Estonia. The drugs were donated by Wyeth,
Ayerst via the WISDOM trial (Women's International Study of Long Duration Estrogen after Menopause), coordinated by Dr. Madge Vickers, London, U.K. We express our sincere gratitude to the trial physicians, trial midwives and women who participated in the trial.
References

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Table 1. Numbers of women by the length of exposure (years) at the time of stopping exposure in the EPHT trial (May 2004).

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<td><strong>Total</strong></td>
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<td>808</td>
<td>597</td>
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Figure 1 Recruitment flow

Postmenopausal women aged 50-64 years. Postal questionnaire including trial introduction, invitation to participate (39 713)

No response, wrong address, dead

Wants to participate (n=6 605)

Found ineligible

Pre-randomization (n=4 295)
(Blind: HT or Placebo, Non-blind: HT or No treatment)

Invited to examination
Blind group (n=2 136)

Invited to examination
Non-blind group (n=2 159)

Found ineligible
No examination visit
No informed consent

Included Blind HT 415

Included Blind Placebo 381

Included Non-blind HT 503

Included No treatment 524

Found ineligible
No examination visit
No informed consent

No response, wrong address, dead
Figure 2. Time flow of the trial

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<th>Other trials</th>
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<td>WISDOM recruitment starts</td>
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<td>Mammogram screening</td>
<td>2001</td>
<td>WHI warns 2</td>
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<td>Recruitment ends</td>
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<td>WHI CEE+MPA exposure ends</td>
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<td>Decision I to shorten exposure</td>
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<td>WISDOM recruitment stops</td>
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<tr>
<td>Exposure ends</td>
<td>2004</td>
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