SIRPA-LIISA HOVI

Preventive Trial on Postmenopausal Hormone Therapy in Estonia

A study of treatment preferences and trial process within a changing environment

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TIIVISTELMÄ

Hovi Sirpa-Liisa. **Preventive Trial on Postmenopausal Hormone Therapy in Estonia — A study of treatment preferences and trial process within a changing environment.** [Ehkäisevä koe vaihdevuosihormoneista Virossa — Hoitomieltymykset ja tutkimusprosessi muuttuvassa ympäristössä.] STAKES, Research Reports, 157. Helsinki, Finland, 2006. ISBN 951-33-1849-4

Vaihdevuosihormoneilla tarkoitetaan sekä estrogeenia että estrogeenin ja progestiinin yhdistelmää, ja tässä työssä hormoni viittaa näihin lääkkeisiin. Ensimmäinen kaupallinen estrogeenivalmiste oli saatavilla jo vuonna 1926. 1970-luvulla todettiin estrogeenin aiheuttavan kohtusyöpää ja syövän estämiseksi alettiin hoitoon lisätä progestiini niille naisille, joiden kohtua ei ollut poistettu. Hormoneja on käytetty vaihdevuosien aikana ja niiden jälkeen erilaisten oireiden lievittämiseen, biologisen vanhenemisen hidastamiseen ja mm. sydän- ja verisuonitautien ja osteoporoosin ennaltaehkäisyyn. Vaihdevuosihormonien käyttö Suomessakin on lisääntynyt ja hoitoaika pidentynyt. Lähes puolet 54–60-vuotiaista naisista sai Suomessa vuonna 2003 sairausvakuutuksesta korvausta hormonihoidosta ja 70-vuotiaistakin naisista vielä 15 %. Vaikka hormonien käyttö on ollut yleistä vuosikymmenien ajan ja hoitoajat ovat olleet pitkiä, yhtään satunnaistettua, kontrolloitua pitkäaikaista tutkimusta vaihdevuosihormonien vaikutuksista ei ollut vielä 1995 tehty. Suomessa tällaisen kokeen tekeminen ei enää 1990-luvulla ollut mahdollista, koska sekä naisten että lääkäreiden mielipiteet estivät satunnaistamisen.

Tämän tutkimuksen päätavoite oli selvittää satunnaistetun kokeen tekemisen mahdollisuutta Virossa, tutkia mieltymyksiä vaihdevuosien hormonihoitoon ja tulosten yleistettävyyttä arvioimalla tutkimusprosessia, joka tehtiin muuttuvassa ympäristössä jo myyntiluvan saaneella lääkkeellä. Tutkimuksen tarkempina tavoitteina oli selvittää ja verrata naisten ja lääkäreiden käsityksiä vaihdevuosista ja heidän mieltymystään hormonihoitoon, verrata kokeeseen haluavien ja ei-haluavien naisten ominaisuuksia, tutkia, onko tutkimusasetelmalla (sokkoutettu tai avoin) vaikutusta naisten osallistumiseen, ja analysoida tutkimusympäristössä tapahtuneita muutoksia.

Itse hormonihoitokoe, EPHT (Estonian Postmenopausal Hormone Therapy trial) on satunnaistettu, kontrolloitu pitkäaikainen vaihdevuosihormonihoitokoe, jossa naiset on arvottu neljään tutkimushaaraan. Näistä kaksi haaraa muodosti perinteisen sokkoryhmän, jossa kukaan ei tiennyt, saiko nainen hormonivalmistetta vai lumelääkettä. Toiset kaksi haaraa muodosti avoimen ryhmän, jossa puolet naisista sai hormonilääkkeen ja toinen puoli ei saanut mitään. Kokeellisella tutkimuksella haluttiin selvittää, onko vaihdevuosihormonien käytöllä vaikutusta terveyspalveluiden käyttöön. Tämän tutkimiseksi kokeessa on myös avoin ryhmä. Lisäksi kokeessa tutkittiin pitkäaikaisen hormonihoidon vaikutusta naisten terveyteen, elämänlaatuun, vaihdevuosikokemuksiin ja sosiaalisiin suhteisiin sekä lyhytaikaisia vaikutuksia naisten hyvinvointiin. Nämä tulokset raportoidaan muualla.

Hoitomieltymyksiin ja naisten osallistumishalukkuuteen vastaamiseksi tehtiin kaksi postikyselyä: vuonna 1998 sai 2 000 virolaista naista kyselylomakkeen ja vuonna 2000 sai 500 virolaista lääkäriä, gynekologeja ja perhelääkäreitä, kyselylomakkeen. Naisilta kysyt-

tiin heidän käsityksiään vaihdevuosista mutta myös terveyskäyttäytymisestä, sairauksista ja lääkkeiden käytöstä sekä halua osallistua hormonihoitokokeeseen. Tämä kysely toimi samalla esitutkimuksena varsinaiselle kokeelle. Naiset rekrytoitiin käyttämällä postikyselyä, mutta varsinainen rekrytointilomake oli suppeampi. Siinä kysyttiin vain sellaisia tietoja, joista voi päätellä naisen täyttävän kokeeseen osallistumiskriteerit. Lääkäreiltä kysyttiin heidän käsityksiään vaihdevuosihormoneista ja heidän tavastaan suositella hormonihoitoja.

Tutkimusasetelman (avoin ja sokkoryhmä) vaikutusta naisten halukkuuteen osallistua kokeeseen tutkittiin analysoimalla rekrytointiprosessia. Kaikkiaan 39 713 naista sai kutsun osallistua kokeeseen ja halukkaista osallistumiskriteerit täytti 4 295 naista, jotka arvottiin neljään eri tutkimushaaraan. Tieto tutkimushaarasta suljettiin naisen nimellä ja tutkimusryhmällä varustettuun läpinäkymättömään rekrytointikuoreen yhdessä lääketietolehden kanssa. Kuoret odottivat naisen valitsemassa tutkimusklinikassa hänen saapumistaan lääkärintarkastukseen. Tutkimusaikaa varatessaan nainen tiesi, oliko hänet arvottu sokkoryhmään vai avoimeen ryhmään. Jos nainen todettiin tutkimuksen jälkeen edelleen sopivaksi osallistumaan ja hän oli edelleen halukas, hän allekirjoitti suostumuslomakkeen yhdessä lääkärin kanssa, ja sitten kirjekuori avattiin. Nainen sai kirjallisen ohjeen ja mahdolliset lääkkeet mukaansa. Jos nainen ei täyttänyt tutkimuksen osallistumiskriteereitä, muutti mielensä eikä allekirjoittanut suostumuslomaketta tai ei saapunut vastaanotolle, hänen kirjekuorensa jäi avaamatta ja tutkimushoitaja merkitsi kuoren päälle, miksi naista ei ollut rekrytoitu. Vuosina 1999–2001 tutkimukseen liittyi 1 823 naista. Lisäksi käytettiin ensimmäisen vuoden seurantakyselyn tietoa naisten syistä osallistua kokeeseen.

Tutkimusympäristön muutoksien analysoimiseksi kerättiin tietoa eri lähteistä: eri kokousten pöytäkirjoista ja muistiinpanoista, tutkimushenkilöstön toimintaohjeista, artikkeleista ja julkaistuista tutkimusraporteista ja kirjeenvaihdosta. Lisäksi aineistoa kertyi tutkijan osallistuvan havainnoinnin muistiinpanoista eri kokouksista ja tapaamisista klinikoiden tutkimushenkilöstön, muun tutkimusryhmän ja kansainvälisten tutkijoiden kanssa. Myös vaihdevuosihormonien myyntilukutietoja käytettiin.

Kyselylomakkeen palautti 1 312 naista (69 %). Virossa hormonien käyttö oli alhaista, vain 3 % kyselyyn vastanneista naisista ilmoitti käyttävänsä vaihdevuosihormoneja. Naisilla ei ollut vahvaa mieltymystä hormonihoitoon, se oli heille vieras asia eikä heillä ollut mielipiteitä hormonien hyödyistä tai haitoista. Puolet naisista piti vaihdevuosia luonnollisena asiana naisen elämässä eivätkä ne heidän mielestään kaivanneet lääkärin hoitoa. Useimmat naiset eivät halunneet hormonihoitoa kaikille naisille, joilla oli vaihdevuosista johtuvia oireita, tai kaikille sairauksia ehkäiseväksi hoidoksi vaihdevuosien jälkeen. Mitä enemmän naisella oli koulutusta, sitä kielteisemmin hän suhtautui hormonihoidon suosittamiseen kaikille naisille. Sen sijaan naiset, jotka olivat käyttäneet lääkkeitä, muitakin kuin vaihdevuosihormoneja, ja/tai joilla oli useita käyntejä terveydenhuollossa, suhtautuivat hyvin myönteisesti hormonihoitoon.

Lääkäreistä 342 (68 %) palautti lomakkeen. He suhtautuivat vaihdevuosihormoneihin paljon myönteisemmin kuin naiset ja suosittelisivat hoitoa paljon useammin kuin naiset haluaisivat. Vain yksi prosentti lääkäreistä piti vaihdevuosia normaalina tilana, joka ei vaadi hoitoa. Gynekologien suhtautumien hormonihoitoihin oli paljon myönteisempi

sempi kuin perhelääkäreiden. Lääkärit olivat lähes kaikki sitä mieltä, että hormonihoito estää osteoporoosia, ja useimmat pitivät sydän- ja verisuonitautien ehkäisemistä ja vanhenemisen hidastumista hoidon etuina.

Esitutkimuskyselyyn vastanneista naisista 17 % oli kiinnostunut osallistumaan tutkimukseen (11 % kaikista kyselylomakkeen saaneista). Halukkaat olivat nuorempia ja heillä oli enemmän terveydenhuoltokontakteja kuin niillä naisilla, jotka eivät halunneet osallistua kokeeseen. Lisäksi halukkailla oli useammin ylipainoa ja krooninen sairaus kuin ei-halukkailla. Halukkaat naiset raportoivat myös muita useammin masennusta ja unettomuutta. Tavallisimmat osallistumisen syyt olivat mahdollisuus lääkärintarkastukseen ja edesauttaa virolaista tutkimusta.

Kaikista kokeeseen kutsutuista 39 713 naisesta 17 % oli kiinnostunut osallistumaan kokeeseen, ja 11 % (n = 4 295) kaikista todettiin kyselylomakkeen tietojen perusteella täyttävän tutkimuksen mukaanottokriteerit. Avoimen haaran lääkärintarkastuksiin tuli enemmän naisia kuin sokkohaaran, ja avoimeen ryhmään rekrytoitiin 30 % enemmän kuin sokkoryhmään. Pääasiallisesti ero johtui avoimen ryhmän naisten suuremmasta mielenkiinnosta osallistua lääkärintarkastukseen. Tarkastuksessa lääkärit totesivat enemmän naisia sopimattomaksi tutkimukseen kuin ennalta sovitut kriteerit olisivat edellyttäneet. Kaikkiaan 1 823 naista rekrytoitiin; se on 5 % koko tutkimusjoukosta.

Muutokset tutkimusympäristössä olivat nopeita. Eniten EPHT-tutkimukseen vaikuttivat muiden samanaikaisesti meneillään olleiden vaihdevuosihormonikokeiden tulokset. Jouduimme kolme kertaa lyhentämään lääkkeen antoaikaa mutta pystyimme saamaan kaikki tarvittavat tutkimustiedot. Yhteiskunnalliset muutokset Virossa olivat nopeita ja vaativat joukon ylimääräisiä neuvotteluja, nopea hintojen nousu uhkasi tutkimuksen varojen riittävyyttä. Toisaalta uuden teknologian tulo helpotti tutkimuksen toteuttamista. EPHT-koe oli mittakaavaltaan pieni, ja se helpotti kokeen joustavaa toteuttamista, lisäksi tutkimusryhmän vahva sitoutuminen auttoi tutkimuksen läpiviemisessä.

Virossa oli mahdollista toteuttaa pitkäaikainen, satunnaistettu, kontrolloitu lääkehoitokoe käyttäen jo myyntiluvan saanutta valmistetta. Naisilla ei ollut vahvaa mieltymystä vaihdevuosihormonihoitoihin, ja se mahdollisti satunnaistamisen. Lääkäreiden, erityisesti gynekologien, mieltymys hormonihoitoihin edesauttoi tutkimuksen toteuttamista.

Odotusten mukaisesti naiset suosivat avointa tutkimusryhmää. Avoimen tutkimusryhmän käyttö pitkäaikaisissa ehkäisevissä kokeissa hyödyttäisi tutkimusta: saataisiin rekrytoitua enemmän osallistujia, kustannukset olisivat alemmat ja kokeen toteuttaminen olisi helpompaa. Lisätutkimusta tarvitaan kuitenkin siitä, miten avoin tutkimusryhmä vaikuttaa tutkimuksen toteutettavuuteen ja tutkimustuloksiin.

Pitkäaikaisen kokeen suunnittelu on vaativaa nopeasti ja jopa odottamattomasti muuttuvassa ympäristössä. Siksi jo suunnitteluvaiheessa hankkeeseen olisi jätettävä liikkumavaraa. Riittävän rahoituksen varmistaminen riippumattomasta lähteestä on välttämätöntä. Tutkimusmetodologiaa pitäisi kehittää ja yrittää löytää vaihtoehtoisia malleja perinteiselle yksilöiden sokkouttamiseen perustuvalle mallille.

Avainsanat: Vaihdevuodet, hormonihoito, satunnaistettu kontrolloitu koe, mieltymys

ABSTRACT

Hovi Sirpa-Liisa. **Preventive Trial on Postmenopausal Hormone Therapy in Estonia – A study of treatment preferences and trial process within a changing environment.** STAKES, Research Reports, 157. Helsinki, Finland, 2006. ISBN 951-33-1849-4

Even though the first commercial oestrogen preparation became available in 1926, by 1995 the long-term effects of postmenopausal hormone therapy (HT) were still debated, and a need for trials existed. To study the preventive effects of HT requires a long duration before effects can be detected. Only a few reports have previously described what happens in long-term trials and the process in practice.

This study investigates women's and physicians' preference for HT and how these issues are relevant to feasibility and generalizability in a preventive randomised controlled drug trial. It further describes the long-term research process in a changing environment. The trial medication was a licensed drug, and it was conducted as a multi-centre trial in a neighbouring country Estonia, in a different medical culture. The Estonian Postmenopausal Hormone Therapy trial (EPHT) is a four-arm trial. Women were invited to participate by means of postal questionnaire that included information about HT and a short description of the trial. Responses provided information about potentially eligible women who were interested in participating. These women were pre-randomised to four arms: two arms in the blind group with active treatment and a matched placebo, and two arms in the non-blind group with open-label HT and control arm with no intervention. All women were invited to a recruitment examination in the group where they were allocated. All recruited women signed the informed consent. In the non-blind group, the allocated arm was revealed after the informed consent was signed. The EPHT trial is registered to the Controlled Clinical trials [ISRCTN35338757].

To study women's preference for HT, a pilot survey for a random sample of 2 000 Estonian women aged 45–64 in 1998 was conducted. The survey provided data to investigate women's perceptions of the climacteric and HT, and to assess their interest in participating in the trial. Decision-making for participation was examined using the notes of the recruitment process for the trial in 1999–2001, and from the one-year follow-up questionnaires for the 1 823 recruited women. To study Estonian physicians' preferences for HT, a survey of a random sample of 500 Estonian gynaecologists and general practitioners was carried out in 2000. Furthermore, sales data of HT, written material, notes from participatory observation, and project correspondence were used to analyse changes during the EPHT trial process.

HT use in Estonia was low, only 3% of the studied women reported current use. Women did not have a strong preference for HT. They were not familiar with HT: they did not have opinions about it and most of them could not take a stand on its health benefits or harms. About half of the women considered the climacteric a normal phase in a woman's life that does not need treatment by a physician, and a woman does not

lose her femininity during the climacteric. Most women disagreed with prescribing HT to all women showing climacteric symptoms or to all postmenopausal women; the more education a woman had the more negative her opinion was on prescribing HT to all women. Women who had used drugs and/or had several visits to health care had a stronger preference for HT.

Physicians' preference for HT was stronger than women's, and physicians would recommend HT to women much more often than women would want. Few (1%) physicians considered the climacteric a normal phase that does not require treatment. Almost all physicians were of the opinion that HT contributes to the prevention of osteoporosis, and most said that the prevention of cardiovascular diseases and delay in ageing were benefits. Gynaecologists had more favourable attitudes than general practitioners (GPs). GPs mentioned more harms for long-term HT than gynaecologists. Gynaecologists would routinely prescribe HT for all women at menopause with no contraindication —regardless of symptoms.

17% of those women who responded to the pilot survey (n=2 000) were interested in joining the EPHT trial (11% of all pilot women). Women interested in joining the trial were younger and had had more contacts with the health-care system (measured by visits to physicians, use of calcium drugs and HT) than non-interested women. Compared to non-interested women, those interested were more often obese, had more frequently some chronic diseases and more frequently reported depression and sleeplessness. Interested women had stronger preference for HT than non-interested women. In the first year follow-up questionnaire, women reported the most common reasons for joining the trial as being the opportunity to obtain medical examination by a trial physician, and the facilitation of Estonian research. The reasons for joining the trial were relatively similar in the blind and non-blind groups.

A total 39 713 questionnaires were sent to invite women to participate in the main trial. Of those invited, 17% were interested in joining and 11% (n= 4 295) were judged to be eligible on the basis of the questionnaire data. These 4 295 women were pre-randomised to four trial arms, two in the blind group and two in the non-blind group. More women decided to come to examination in the non-blind than the blind group, and the final recruitment rate was 30% higher than in the blind group mainly due to women's varying decisions to come to the recruitment examination. At the examination the number of women defined as ineligible by physicians and excluded before study inclusion was larger than the number of women with pre-determined reasons for exclusions. A total of 1 823 women signed the informed consent, 5% of the whole sample population.

The research environment changed rapidly. Results from other trials had the most effect on EPHT, as they led to us shortening trial treatment three times, but the trial was long enough that we could obtain all the necessary data. Rapid changes in the society led to a lot of extra negotiations. Rapid increases in prices caused an extra financial burden for the trial. However, new technology made many things happen much easier than at the

beginning of the trial. As a small scale trial, the EPHT was flexible and people involved in the trial put a lot of effort into keeping the trial going on. It was planned that the trial protocol would follow Estonian practice on HT.

It was feasible to establish a long-term preventive, randomised controlled trial of HT in Estonia using licensed medication. Women had not formed an opinion of HT and they had no preference for HT which made the randomisation possible. Physicians had strong preference for HT, especially gynaecologists, which did facilitate the trial.

As we expected, women favoured the non-blind study group over the blind design. Using a non-blind controlled design in long-term preventive trials would bring benefits for research: more participants could be recruited, costs would be notably lower, and running the trial would be easier. More research is needed on how blinding influences study feasibility and results.

Planning a long-term trial is demanding. Currently it can be expected that society changes quickly and even unexpectedly. Thus, already at the planning stage some flexibility should be built in the project. Sufficient financing from independent sources are needed. Trial methodology should be developed to find alternatives to traditional blind, individually randomised designs.

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Maturitas 2005;51:413–425. doi:10.1016/j.maturitas.2004.11.001

II Sirpa-Liisa Hovi, Tiina Karttunen, Helle Karro, Elina Hemminki.
Comparison of Estonian and Finnish physicians' opinions of menopause and hormone therapy. Maturitas 2004;49:107–113. doi:10.1016/j.maturitas.2003.11.004

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V Sirpa-Liisa Hovi, Piret Veerus, Mati Rahu, Elina Hemminki.
Experiences of a long-term randomised controlled prevention trial in a maiden environment: Estonian Postmenopausal Hormone Therapy trial. Submitted for publication

List of abbreviations

ATC	Anatomical Therapeutic Chemical
DDD	Daily Defined Dose
EKMI	Institute of Experimental and Clinical Medicine (Experimentaalse ja Kliinilise Meditsiini Instituut)
EPHT	Estonian Postmenopausal Hormone Therapy Trial
EPT	Estrogen-progestogen Therapy
ET	Estrogen Therapy
FDA	United States Food and Drug Administration
FP	Family Practitioner
GP	General Practitioner
HRT	Hormone replacement therapy
HT	Hormone Therapy
OC	Oral Contraceptives
PHT	Postmenopausal Hormone Therapy
RCT	Randomised Controlled Trial
STAKES	National Research and Development Centre for Welfare and Health
TAI	National Institute for Health Development (Tervise Arengu Insituut)
WHI	Women's Health Initiative
WISDOM	Women's International Study of Long Duration Oestrogen after the Menopause

1 Introduction

Menopause strictly means the final menstruation. Natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. It is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathologic or physiologic cause (WHO, 1996). Surgical menopause occurs after uterus and/or both ovaries are removed. The age at which natural menopause occurs in Western countries is around the age of 50 (McKinlay et al., 1992), though the use of hormone therapy, removal of uterus and ovaries confuses these definitions (Topo et al., 1995a). The climacteric is the phase in the ageing of women marking the transition from the reproductive phase to the nonreproductive state. These phases together incorporate the perimenopause by extending for a longer variable period before and after perimenopause (Utian, 1999). Menopause is used in this study mainly as an adjective, such as in "menopausal symptoms", while the climacteric is used to define the time around menopause. The climacteric is near the lay terms "üleminekuiga" in Estonian or "vaihdevuodet" in Finnish. These local language-specific words were used in the questionnaires sent to the women.

Oestrogens are female hormones responsible for gender development and ruling gender functions in a growing foetus and a pubertal girl. They affect almost every part of the female body. Oestrogens production begins at puberty with production mainly in the ovaries. Oestrogen levels remain high during the entire reproductive life. The ovaries are active until the middle-age when production dies down and menstruation ceases. The most important of the gestagens is progesterone which is secreted mainly from the corpus luteum and effects both the endometrium in the uterus and the breasts. It is necessary for the continuation of pregnancy. If the pregnancy does not start, secretion of progesterone ends and the thickened endometrium causes menstrual bleeding. In postmenopause, progesterone is most consistently absent (Punnonen, 2004).

Treatment with oestrogen or with a combination of oestrogen and progestin in postmenopause has been called hormone replacement therapy (HRT), giving the impression that something missing should be substituted. However, the low level of oestrogen of middle-aged women is physiological. That is why in this thesis terms "hormone therapy (HT)" or "postmenopausal hormone therapy (PHT)"

have been used. Further, the North American Menopause Society has recommended in its statement the acronym ET for oestrogen therapy and EPT for combined oestrogen-progestogen therapy (NAMS, 2004).

Oestrogens have been in use for decades. The first commercial oestrogen preparation became available in 1926 and in 1932 oestrogen treatment was first mentioned to prevent and treat climacteric syndrome (Wilbush, 1979). When synthetic oestrogen was discovered it provided a relatively cheap way of producing oestrogen-containing drugs, and in 1942 the oestrogen preparation Premarin® was brought to the market by Wyeth for the treatment of menopausal symptoms(Stefanick, 2005).

In 1963 it was mentioned that oestrogen could slow the ageing process and that every woman should take HT for as long as she lived (Wilson et al., 1963). This knowledge was effectively distributed to lay women in the USA and Europe, especially in Germany and in the United Kingdom (UK), but also in the Finnish lay press (Topo, 1997b). In 1972 the Food and Drug Administration (FDA) in the USA announced that oestrogens were "probably effective" for the prevention of osteoporosis (Stefanick, 2005).

The harms of oestrogen began to emerge and a risk of endometrial cancer after seven or more years of oestrogen use was found in the 1970s (Ziel et al., 1975). In the 1970s the trial arm with oestrogen in the Coronary Drug Project randomized trial in men with coronary heart disease was stopped due to early excess clotting and cardiovascular disease, and at the same time a risk of blood clot and stroke was reported in young women taking (high-dose) oral contraceptives (OC) (Stefanick, 2005). The collapse of oestrogen sale started in 1976, with prescriptions falling 59% from 1974 to 1979 (Hemminki et al., 1988), and oestrogen product (Premarin®) fell from the second most frequently prescribed drug in 1975 in the USA to 25th position in 1979 (Swartzman et al., 1987). After progestin was added to oestrogen to prevent endometrial cancer (Wentz, 1974) sales of oestrogen and progestin started to increase again (Hemminki et al., 1988).

In the mid-1970s it was shown that oestrogen therapy for preventing bone loss in the early postmenopausal period resulted in fewer fractures (Weiss et al., 1980), and in the 1980s women were advised to get hormone treatment as soon as possible after the menopause to prevent osteoporosis (Cooper, 1990). Since the late 1970s many observational studies supported the hypothesis that because those women dying of cardiovascular diseases do so ten years later than men it must be due to oestrogen's preventive effect (Adam et al., 1981; Bain et al., 1981; Beard et al., 1989; Pfeffer et al., 1978; Ross et al., 1981; Stampfer et al., 1991a; Stampfer et al., 1985; Talbott et al., 1977; Thompson et al., 1989). A meta-analysis of non-experimental studies also showed support to this idea (Stampfer and Colditz, 1991a). However, sceptical opinions occurred stating that the protective effect could be due to the selection bias (Barrett-Connor, 1998b; Derby et al., 1995; Hemminki et al., 1993b).

New issues about HT were emerging such as the risks and benefits of therapy, questions about the safety and efficacy of prescribed regimens, and the identification of subgroups of women for whom hormone therapy may be particularly appropriate or inappropriate (Barrett-Connor, 1998a; Hemminki, 2000; Hemminki et al., 1997a). In 2002 meta-analyses of pooled data from the five observational studies of CHD incidence, adjusted for socioeconomic status, showed no protective effect of hormone therapy (Humphrey et al., 2002).

Physicians played a very important role in the health care technology invasion in Finland: in the HT debate they blended medical knowledge with their personal views, and this included strong normative claims about what a woman should be and look like (Kangas, 1997; Topo, 1997a; Topo, 1997b). Physicians' positive attitude towards HT increased prescribing (Andersson et al., 1998; Newton et al., 2001), and physicians tend to recommend HT more often than women want (Topo et al., 1993). Physicians' own and their spouses high use of HT reflects a favourable attitude to HT (Andersson et al., 1998; Isaacs et al., 1997; Nilsen et al., 2001), even in spite of recent non-beneficial research results (Isaacs et al., 2005). HT users visit a gynaecologist more often than non-users (Ekstrom et al., 2003; Hundrup et al., 2002; Mueller et al., 2002) and physicians' recommendations to use HT does influence women (Lewin et al., 2003; MacLaren et al., 2001; Rozenberg et al., 1997b; Sogaard et al., 2000; Topo et al., 1993).

By 1995 postmenopausal hormone therapy had been in use for decades but the long-term effects were still debated, and the need for long-term trials existed. A lot of clinical trials have been conducted in order to produce data on HT's short-term effects on different symptoms, most often on vasomotor symptoms with various oestrogens and with various routes. Exposure time in these studies has been short, from some weeks to a couple of months.

The planning of our trial in Estonia was started in 1995. In 1992 a study of HT was conducted in Finland in the Tampere area (Hokkanen et al., 1997) with the aim of finding out if a preventive randomised trial can be conducted as a part of the normal health care practice. The study would not have been easy to carry out: women had strong opinions about HT, either they did not want to stop the previous HT or they did not want to follow the recommendation to start HT if they had not done it earlier, and many women had difficulties stopping the treatment because their symptoms returned. Furthermore, gynaecologists were not willing to follow the recommendations that their clients had received (Hokkanen et al., 1997). HT use in Finland in 1989 among postmenopausal women was 19% (Topo et al., 1991), and in 1995 already 27% (Topo, 1997b).

In Estonia, Finland's southern neighbour country (Figure 1) HT had not yet become an established practice at the beginning of the 1990s. As found in Hokkanen et al. (1997) an established HT medication makes treatment adherence difficult, because women want to choose their medication, as happened in Fin-

FIGURE 1. Map over Finland and Estonia.

land (Hokkanen et al., 1997). In Estonia HT sales measured as daily defined doses (DDD) in 1995 were 1.96 per 1000 inhabitants (Riigi Ravimiamet, 1996) compared to nearly 40 in Finland. (Lääkelaitos, 2005).

Currently hormone therapy is common. In Finland, in 2003 about 46% of the women aged 54–60 years received compensation at least once from the Sickness Insurance because of systemic HT, and still, at the age of 70, 15% of the women received compensation. In addition local preparations were compensated, but because some local preparations are over-the-counter drugs, they remain uncompensated. The Sickness Insurance paid 38% of the costs to women and women paid EUR 21 million themselves in 2003. Estradiol was third on the list for the most sold prescriptions in Finland (Martikainen, 2004).

At the beginning of the year 2000 more than 100 million women worldwide used HT, with a financial value about EUR 3.4 billion euros (Clark, 2003), so it is a significant market for the pharmaceutical industry. Mainly HT users live in North America, Australia, and Northern and Middle Europe, less in Southern Europe, although within countries HT use varies between areas (Keating et al., 1999).

If HT has beneficial effects on cardiovascular diseases, as non-experimental studies suggests (see e.g. (Stampfer and Colditz, 1991a) it should be available for all women. Randomised comparisons provide the most rigorous assessment of the therapeutic effect of particular interventions. McPherson (1994) argues that the extent of true uncertainty should be decisive when setting research priorities. Notable variations between areas indicate true clinical uncertainty. The formal method for assessing priorities for research rests on experts expressing their own uncertainties. When these uncertainties are explicit the ethical basis for randomisation is widely accepted. Currently decision-making has explicitly to take account of two important concepts, first the role of supplier-induced demand, and secondly, how to accommodate consumer preferences into decisions (McPherson, 1994). In the 1990s evidence about HT's possibly harmful effects began to accumulate and the need for a preventive RCT on HT emerged (Hemminki, 2000).

To study the preventive effects of HT, often with licensed medication, requires a trial of long duration before the effects, both beneficial and harmful, can be detected. The long duration of a trial brings more demands to the study. Very few reports have described what happens in long-term trials and the process in practice; the study process has remained something of a black box. When the processes are not described publicly, knowledge of them does not accumulate. Especially in trials that fail to meet their targets, information about the process is important to prevent other researchers from making similar mistakes.

To be clinically useful the results of the RCT must also be relevant to a definable group of people, i.e. the results must be applicable or generalisable. Trial participants' or physicians' preferences can be a threat to generalizability. Preference to treatment can be controlled using a placebo. However, in a long-term preventive trial using a placebo may decrease recruitment.

The purpose of this thesis was to study the feasibility of conducting a preventive randomised controlled trial on postmenopausal hormone therapy with regard to women's and physicians' preferences for HT, and to describe the long-term study process in a changing environment. Women were randomized to four arms: two arms in a blind group, and two arms in a non-blind group. The intervention drug was already a licensed medication. A series of five articles will be summarised here and they are referred to with the Roman numerals I–V. The data describe both middle-aged women's (Articles I, III) and physicians' (Article II) perceptions of the climacteric and preferences for HT, the effect of the trial design on participants' decision-making in the recruitment process (Article IV), and analyse the changing research environment and the entire research process (Article V).

2 Review of literature

2.1 Preference framework in a randomized controlled trial

Randomized controlled trials (RCTs) provide the most reliable evidence for treatment efficacy. Although trial participants are often conceptualized as passive recipients of interventions, many have preferences for treatments under evaluation and may decline to consent to randomization. This may reduce the external validity by limiting the generalizability of the results. This is particularly important in a situation where the trial treatment is available outside the randomised trial, as is the case in the IV phase trials with registered drugs. In these cases, treatment providers may also have preferences that effect recruitment. As the trial participants become more active participants in research, the issue of preference is crucial for continued confidence in the results of randomized trials. A strong preference on the part of both the trial participants and the physicians may endanger the trial [see e.g.(Hokkanen et al., 1997)].

The Oxford dictionary definition of prefer is 'to like something better than another: to tend to choose'. This underlines that preferences in the context of RCTs involve two processes: an evaluation of the intervention in terms of its desirability; and the choice between alternative interventions based on this evaluation. (Bower et al., 2005; King et al., 2005) There are no standard tools to evaluate preference in the RCT. The development of a participant's preference can be defined in four stages: information, psychological processes, global preference, and decision-making about randomisation. (Figure 2.1.1)

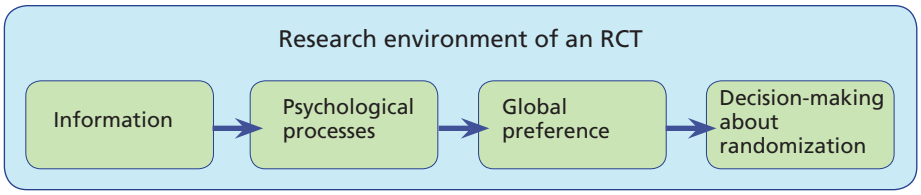

FIGURE 2.1.1 Framework of the preference development in a randomized controlled trial

Preferences are hypothesized to be based on expectancies concerning the process and outcomes associated with the intervention and the perceived value placed on those outcomes and processes. However, participants' preferences may be based on insufficient or incorrect information. In addition, the decision about treatment choice may not always accord with preferences and may be influenced by clinicians, relatives or friends (King et al., 2005). Results from psychological processes are evident in participants' attitudes towards the intended treatment. A global preference can be distinguished in participants' interest to participate in the trial, and actual decision-making manifests in the recruitment process ending either in the signing of an informed consent or not.

If recruitment and participation in RCTs are biased because of preferences, the external validity may be compromised, as the particular population recruited to the RCT (who may have no preferences and agree to randomisation) may not be representative of the population to which the results are to be applied. Preference effect on recruitment can act at the level of patient, practitioner or centre. The requirement of informed consent means that RCT participants almost always have information about the alternative interventions under investigation, and preferences for particular interventions may mean that patients refuse to enter the RCT and risk allocation to their non-preferred treatment (King et al. 2005).

Information about interventions may derive from a number of sources (both outside the immediate context of the RCT and the RCT informed consent procedures) and participants may receive differing amounts of information. This information will lead to various expectancies about the process and outcome of an intervention. The relationship between expectancies, values and preferences is potentially complex. Both direct and indirect preference-treatment interactions are possible even when preferences are based on incorrect information or faulty reasoning because it is the strength of the preference that may be of importance in determining the preference interaction , rather than the validity of the expectancies on which it is based. These all influence participants' decision-making about consenting to randomization (King et al. 2005).

Preferences relate to expectancies concerning the process and outcome of interventions and the perceived value of those processes and outcome. The EPHT trial offered women a medical examination at recruitment and also during the trial for those who consented to the annual examination and trial drugs in the treatment arms. Participants' preferences are important in a situation where the trial intervention is available outside the trial as is the case in a IV phase drug trial where the studied medication is already licensed. Professional preferences are noteworthy because participants tend to follow their physicians' recommendations.

2.2 Women's perceptions of the climacteric and preference for HT

Because most of the information on the menopause and climacteric comes from studies in the industrialized world, mainly from the North America and Europe, with some from Australia, the literature review was restricted mainly to these countries. The review concerns the situation prior to 2002—mainly studies from the 1990s and later—which is when the EPHT trial was planned and carried out, and also before the Women's Health Initiative (WHI) oestrogen-progestin trial (n=16 608) results changed the whole research climate in 2002.

2.2.1 Use of HT and users' characteristics

In the twenty years leading up to 2002, data from various countries show a notable increase in HT use, most substantially in the 1990s. However, comparing HT use between different countries is difficult because of the use of different age-groups and different populations. Sometimes population represents only one part of the country explaining varying results in the studies.

In Finland HT use has long been followed using both representative population samples (Hemminki et al., 1998; Hemminki et al., 1997b; Topo et al., 1991; Topo et al., 1999) and sales statistics. In 1976, HT use was 7% among women aged 50–54 years but started to increase rapidly in the 1980s: already in 1989, 28% of women in this age-group used HT (Topo et al., 1991), with sales figures confirming this increased use (Topo et al., 1995b) (Table 2.2.1.1). In 1995, HT use among women aged 50–54 had further increased to 38% (Hemminki and Topo, 1997b). At the beginning of the 2000s HT use has been around 40% among women aged 50–54 years but starting from the mid 1990s the treatment time has lengthened and lately it has been even more common among women aged 55–64 years than among younger women; in 2001 almost half of the women aged 60–64 years reported HT use in Finland (Sulander et al., 2001; Topo, 2004). Use in Eastern European countries is low e.g. in Poland, use was 12% in 2002 (Rachon et al., 2004).

In Sweden the trend in HT use has paralleled Finnish HT sales, although at a slightly slower rate until the beginning of the 1990s, when Sweden had reached the Finnish level of HT sales (Topo et al., 1995b) and in surveys HT use in women around 55 years had reached about 35%. In Norway the level of current use of HT had been clearly lower than in other Nordic countries, being still less than 10% at the beginning of the 1990s, though it increased rapidly thereafter, with sales statistics showing a more than threefold increase (Sogaard et al., 2000). In Norway, the increased use of HT was not obvious in surveys but in sales statistics the increase has been prominent compared to other Nordic countries. However, in Sweden in 1999, HT sales started to decline among women under 55 years (Socialstyrelsen, 2002).

TABLE 2.2.1.1 Trend of HT use in different countries

Country, Authors	Year	Sample (n)	Age, years	Current HT use, %
Finland				
Topo et al. 1991	1978–80	1 565	45–49	6
			50–54	13
			55–59	8
			60–64	3
			45–64	8
Topo et al. 1991	1989	1 644	45–49	10
			50–54	28
			55–59	24
			60–64	14
			45–64	19
Hemminki & Topo 1997	1995	747	45–49	8
			50–54	38
			55–59	41
			60–64	27
			54–64	27
Helakorpi et al. 1997	1997	798	45–54	25
			55–64	37
Helakorpi et al. 1999	1999	719	45–54	24
			55–64	41
Sulander ym. 2001	2001	802	45–49	14
			50–54	38
			55–59	46
			60–64	46
			45–64	35
Sweden				
Bengtsson et al. 1981	1974–75	1 462	44	3
	1974–76	1 462	52	7
Berg et al. 1985	1982	1 246	52,54	7
Stadberg et al. 1997	1992	4 504	46–62	21
Bardel et al. 2002	1995	2 991	35–64	15
Hammar et al. 1996	1995	1 109	55–56	35
Li et al. 2000	1996	3 900	50–63	32
Thunell et al. 2005	1998	5 411	46–62	31
Ekström et al. 2003	2000–01	564	45	7
			50	27
			55	36
			60	31
			45, 50 ,55, 60	24

TABLE 2.2.1.1 continued

Country, Authors	Year	Sample (n)	Age, years	Current HT use, %
Norway				
Holte 1991	<1991	1 886	45–55	9
Søgaard et al. 2000	1994	565	45–59	21
Søgaard et al. 2000	1996	460	45–60	22
Bakken et al. 2001	1996–97	18 199	45–64	27
Søgaard et al. 2000	1998	489	45–61	23
Denmark				
Køster 1990	1987	526	62	22
Hundrup et al. 2002	1993	14 071	50+ nurses	23
Oddens et al. 1997	1994	1 459	45–65	18
Great Britain				
Griffits et al. 1995	1993	1 255	45–64	20
Lancaster et al. 1995	1993	2 964	45–64	15
Banks et al. 1996	1994–95	1 388	50–64	29
Ballard 2002	1999	413	51–57	42
Strothmann et al. 2003	2003	2 012	45–75	19
Scotland				
Sinclair et al. 1993	1991	1 170	postmenopausal	9
Garton et al. 1995	1992	481	45–49	14
Porter et al. 1996	<1996	6 096	45–54	19
Lewin et al. 2003	2000	461	20–69	17
France				
Ringa et al. 1992	1986	5 266	45–55	8
Fauconnier et al. 2000	1996	561	51	44
Germany				
Mueller at al. 2002	1994–95	1 026	45–64	23
Italy				
Manzoli et al. 2004	1999–2001	8 533	50–70	7
Netherlands				
Groeneveld et al. 1994	1990	1 947	45–60	12
Barentsen et al. 1994	1993	234	45–64	12
Poland				
Rachon et al. 2004	2002	764	45–64	12
USA				
Derby et al. 1993	1981–82	3 279	40–64	5
	1989–90	3 279	40–64	11
Egeland et al. 1988	1983–84	2 137	40–52	6
Harris et al. 1990	1986–87	954	50–65	32

TABLE 2.2.1.1 continued

Country, Authors	Year	Sample (n)	Age, years	Current HT use, %
Keating et al. 1999	1995	495	50–74	38
Rabin et al.1999	<1999	1 966	>50	28
Brett et al. 2003	1999	9400*	40+	24
		*with uterus	40–44	4
			45–49	10
			50–54	30
			55–59	33
			60–64	21
			65–69	16
			70–74	12
			75+	12
Finley et al. 2001	<2001	469	50–70	40
Canada				
Kaufert &Gilbert 1986	1983	2 500	40–59	15
Australia				
Shelley et al. 1995	1991	1 897	45–55	21
MacLennan et al. 1993	1991	1 047	40+	14
O'Connor et al. 1993	<1993	381	45–54	21
MacLennan et al. 1998	1995	3 016	>50	26

In the UK, a 1981-90 cohort study of nearly 20 000 women showed that ever use of HT in women's lives had increased threefold in all 5-year age groups between 45–64 years, with current use being 9% in 1990 (Moorhead et al., 1997). In Great Britain surveys have given as high rates of HT use as in Nordic countries except in Scotland where reported HT use has been under 20 percent during the whole 1990s. HT use in Middle Europe varies a lot between different countries, studies in France (Fauconnier et al., 2000; Gayet-Ageron et al., 2005) and Germany (Mueller et al., 2002) show high use of HT whereas HT use among 50–54 years old women was lower in Spain (Benet Rodriguez et al., 2002), Italy (Manzoli et al., 2004), Poland (Rachon et al., 2004), and Estonia (Hemminki et al., 2004).

In the USA, HT use became popular in the 1970s, although use declined in the mid-1970s after HT was claimed to cause serious, though rare, adverse effects, such as uterine cancer, but it increased rapidly again in the 1980s (Hemminki et al., 1988; Wysowski et al., 1995). HT use in the USA varies by geographic region: women in the South and the West were more likely to be current HT users than women in the Northeast (Brett et al., 2003b; Hemminki et al., 1988; Keating et al., 1999). The MONIKA-study found similar geographical differences in Europe (Lundberg et al., 2004).

Early on women with more education were much more likely to be HT users than those with less education (Brett and Reuben, 2003b; Finley et al., 2001; Friedman-Koss et al., 2002; Keating et al., 1999; Levy et al., 2003; Li et al., 2000; Mueller et al., 2002; Thunell et al., 2005). However, when HT use became common, the level of education was no longer such a strong predictor of HT use. This has been reported from Finland (Topo, 1997b; Topo et al., 1999), Norway (Bakken et al., 2001) Sweden (Ekstrom et al., 2003; Li et al., 2000) and Scotland (Lewin et al., 2003).

High income level was also associated with common HT use (Bakken et al., 2001; Finley et al., 2001; Keating et al., 1999; Levy et al., 2003; Brett and Reuben, 2003b; Finley et al., 2001; Friedman-Koss et al., 2002; Keating et al., 1999). HT users had more visits to the gynaecologist than non-users (Ekstrom et al., 2003; Hemminki et al., 1993a; Hundrup et al., 2002; Levy et al., 2003; Mueller et al., 2002).

Woman's ethnicity affects HT use, with white ethnicity predicting HT use (Brett and Reuben, 2003b; Finley et al., 2001; Friedman-Koss et al., 2002; Keating et al., 1999). Black women were only 30% as likely as white women to ever use HT (Levy et al., 2003; MacDougall et al., 1999; Marsh et al., 1999) and Mexican-American women were less likely than white women to ever use of HT (MacDougall et al., 1999). Most studies on HT use among different ethnic groups have been performed in the USA. Black women were also significantly less likely than white women to be advised about HT in the USA (Weng et al., 2001), but also in an area with several ethnic groups in South London, UK, white women were more likely to be HT users than other ethnic women (Harris et al., 1999).

Previous oral contraceptive (OC) use has been reported in several studies as being more likely among ever users than those that have never used HT (Bakken et al., 2001; Hundrup et al., 2002; Lewin et al., 2003; Levy et al., 2003; Li et al., 2000) and women with a previous hysterectomy were more likely to be HT users than women with an intact uterus (Bakken et al., 2001; Finley et al., 2001; Keating et al., 1999; Lancaster et al., 1995; Lewin et al., 2003; Moorhead et al., 1997; Salamone et al., 1996). In a Swedish study, being on medication and the number of medications were associated with HT use. The women using anti-depressive medication, cardiovascular drugs or drugs for acid-related symptoms were found to be more frequently current HT users (Ekstrom et al., 2003). Women who used supplemental calcium were more likely than other women to use HT (Hundrup et al., 2002; Keating et al., 1999).

In a study on Danish nurses, HT ever users more often reported very poor or poor health than never users, but compared to an age-matched group of Danish women the nurses had a healthier lifestyle, were physically more active, and had healthier eating habits (Hundrup et al., 2002). The healthy-user phenomenon was obvious in other studies as well (Bakken et al., 2001; Hemminki et al., 1993a; Mueller et al., 2002). Having had a Pap smear and mammogram screening were associated with HT use (Finley et al., 2001; Mueller et al., 2002).

In the 1990s in the USA, Keating et al. (1999) did not find smoking status, family history of myocardial infarction, personal history of hypertension, elevated cholesterol level or personal history of angina or myocardial infarction had any effect on HT use (Keating et al., 1999), but in Finley et al. (2001), study women with known cardiovascular disease were unlikely to use HT (Finley et al., 2001), while fewer diabetic than non-diabetic women have been found to use HT (Keating et al., 1999) as well as women with no history of breast cancer (Levy et al., 2003).

In low-HT-use countries like Italy and Poland, HT users had better education than non-users, and they had better knowledge about HT (Manzoli et al., 2004; Rachon et al., 2004); they had more likely undergone hysterectomy and had previous OC use than HT non-users (Manzoli et al., 2004). In Japan HT use was rare and the highest prevalence was among women with hysterectomy, women who participated in cancer screenings and women who used calcium supplements (Nagata et al., 1996). In Hong Kong better knowledge about HT was associated with higher education, higher income and more climacteric complaints (Lam et al., 2003).

2.2.2 Women's perceptions of the climacteric

In a Swedish study current HT use was strongly associated with positive attitude whereas a negative attitude towards HT was more prevalent among former HT users (Ekstrom et al., 2003). In Norway, well-educated women had an ambivalent attitude: they had the best knowledge on oestrogen's preventive effect and the highest proportion with the opinion that HT increases quality of life, but at the same time they claimed that scientists know too little about HT effects. Information from the media was associated with a larger degree of scepticism: almost 70% of the women believed that there is too little scientific knowledge about oestrogen and more than 50% agreed totally or partly that oestrogen has several side effects (Sogaard et al., 2000). In the countries where HT use is common, the majority of women agreed that women with distressing symptoms should take HT, although many agreed that natural approaches were better than HT (Lewin et al., 2003; Sogaard et al., 2000; Topo et al., 1993).

In the 1990s in Scotland, women's attitudes have changed and current users agreed less strongly that "menopause should be viewed as a medical condition and treated as such" and also disagreed more strongly that "a woman feels less of a woman after menopause" (Lewin et al., 2003). In the USA women have become less persuaded to take HT, both past users and pre-menopausal women, yet half of never users would follow a doctor's recommendation to take HT (Finley et al., 2001; MacDougall et al., 1999).

Women's knowledge about the climacteric and HT varied between countries and between the studies. Belief in the effects of HT were associated with women being aged 45–59, being informed by a physician, having a high level of education

and currently using HT, which are consistent with the findings in observational studies (Sogaard et al., 2000). When women's knowledge has been investigated, the answers given reflect hypotheses from observational studies, even though we now know that the cardioprotective effect might not be true (Hulley et al., 1998; Rossouw et al., 2002).

Knowledge of the effects of HT on breast cancer, uterine cancer, and heart diseases was low among women in the USA in 1993 (MacDougall et al., 1999). In Scotland in 2000, a majority of women did not know that oestrogen alone may decrease the chance of a heart attack (as was the hypothesis at that time), that oestrogen increases the risk of uterine and breast cancer and that oestrogen is safer for women with a uterus if a progestogen is taken with it (Lewin et al., 2003).

Women's ethnicity had an impact on women's awareness of and attitudes towards HT: white women in the age-group 50–59 with high education were most aware of HT (Lewin et al., 2003; Lydakis et al., 1998; Sinclair et al., 1993), whereas rural Navajo and newly immigrant Latina women had not even heard of HT, and were related to few or no menopausal symptoms with natural menopause or after hysterectomy (Mingo et al. 2000).

Women's awareness about the decreasing risk of osteoporosis during HT was good (Clinkingbeard et al., 1999; MacDougall et al., 1999; Sogaard et al., 2000; Thunell et al., 2005). In Norway in 1994 almost half thought that oestrogen reduces the risk of acquiring osteoporosis (Sogaard et al., 2000); in Scotland postmenopausal ever users of HT agreed more often than never users that lack of oestrogen is a risk factor for osteoporosis (Lewin et al., 2003).

In the USA in 2000, 64% reported osteoporosis prevention as a reason to use HT (Finley et al., 2001) but 55% of white women over 65 years participating in the Multicenter Study of Osteoporotic Fractures never started HT because of a fear that the medication was harmful (38%) or that they felt they did not need it (30%) (Salamone et al., 1996). In Sweden half of women used HT for the prevention of osteoporosis, and 31% used HT for the prevention of cardiovascular disease (Li et al., 2000), whereas in a national survey among Danish women, HT had hardly ever been used as a preventive for osteoporosis (Oddens and Boulet, 1997).

Women's knowledge about chronic diseases increasing after menopause was modest in the USA (Clinkingbeard et al., 1999; MacDougall et al., 1999; Sogaard et al., 2000; Thunell et al., 2005). In Sweden in the 1990s almost half of postmenopausal women believed that HT decreased the risk of cardiovascular disease, a fifth believed that HT decreased the risk of venous thrombosis but two thirds of postmenopausal women said that HT increased the risk of breast cancer, and women in the 46 and 50 year -age cohorts were apprehensive for worsened morbidity and quality of life (Thunell et al., 2005). In Norway in 1994 more than a third of women believed that HT reduces the risk of getting a myocardial infarction and a third answered that HT reduces the risk of breast cancer (Sogaard et al., 2000).

It seems that women start their HT treatment because of menopausal complaints but the use changes into long-term use. In Sweden (Li et al., 2000; Thunell et al., 2005) and in the USA in 2000, a majority of the women reported alleviation of menopausal symptoms as a reason to use HT (Finley et al., 2001; Levy et al., 2003; MacDougall et al., 1999), and even two fifths of US women over 65 years participating in the Multicenter Study of Osteoporotic Fractures reported primary reasons for current HT use as alleviation of menopausal symptoms (Salamone et al., 1996).

In Sweden in 1998, 31% of women aged 46–62 years reported increasing well-being as a reason for starting HT and 22% of the women would consider HT for the rest of their lives despite withdrawal bleeding, while 44% were willing to use HT for the rest of their lives providing bleedings did not occur, while 25% of women over 65 years used HT in Sweden (Thunell et al., 2005). Current HT users reported higher frequencies than non-users for all symptoms except vasomotor symptoms, worse perceived health (Bardel et al., 2002) and higher frequencies of climacteric symptoms (Li et al., 2000; Oddens and Boulet, 1997).

Less is known about the reasons for discontinuation. In Sweden the most common reasons were weight gain, fear of cancer, bleeding, breast tenderness and emotional problems (Li et al., 2000), in Finland in 1989, the reasons given by women for stopping HT supported the notion that women considered HT only as a symptomatic therapy meant only for a certain duration (Hemminki et al., 1993a). In Estonia in the EPHT trial women's reasons for discontinuation most often were side effects and their own choice to stop (Vorobjov et al., 2005).

2.3 Physicians' perceptions on the climacteric and preference for HT

2.3.1 Physicians' perceptions on climacteric

Physicians' attitudes towards the climacteric and HT do not differ very much between the western countries but they differ between speciality and gender. Newton et al. (2001) found that providers, guided by their own practice beliefs, have a profound influence on women's use of HT: the tendency to encourage HT use and the belief that HT prevents CHD in women were positively related to HT prescribing frequency (Newton et al., 2001), while gynaecologists believed more strongly in HT benefits than GPs and internists (Hemminki et al., 1993c; Saver et al., 1997). In the UK both Asian and Caucasian GPs had a positive attitude towards HT (Gupta et al., 2001).

Gynaecologists hold more positive attitudes to HT in the USA (Baron et al., 1998; Exline et al., 1998; Rolnick et al., 1999; Saver et al., 1997), Norway (Nilsen et al., 2001), Sweden (Andersson et al., 1998; Nilsen et al., 2001), Finland (Hem-

minki et al., 1993c), and England (Norman et al., 1994) than do other physicians. Gynaecologists are more likely to recommend HT for long-term use (Hemminki et al., 1993c; Andersson et al., 1998), while in Sweden and Norway, older age of gynaecologists increased the proportion of those recommending HT for long-term use but that was not the case in Denmark (Nilsen et al., 2001). In Washington State in the USA female providers prescribed HT more frequently than male providers (Newton et al., 2001).

All studies on physicians' HT use show that physicians use HT more often than the population they serve. In Sweden HT use among peri- or postmenopausal female gynaecologists and GPs and their spouses was common although significantly higher in gynaecologists and their wives compared to GPs and their spouses, and higher than for other women (Andersson et al., 1996; Andersson et al., 1998; Nilsen et al., 2001). In the UK (Isaacs et al., 1997; Isaacs et al., 2005), in the USA (Frank et al., 2003; McNagny et al., 1997), in Israel (Kaplan et al., 2002), and in Brazil physicians' own use was more common than among the general population (Filho et al., 2005). In the UK, Caucasian and Asian female GPs' views were compared: 78% of the GPs intended to use HT for 5-10 years. Most of them gave the reasons for use as menopausal symptoms and long-term protection from osteoporosis and ischaemic heart disease. More Asian than Caucasian GPs felt that fear of breast cancer would influence their decision (Gupta et al., 2001).

2.3.2 Prescribing for HT

There are many controversies about indications for HT and these controversies obviously exist among physicians. In the USA in 1992 guidelines were given for counselling all postmenopausal women about preventive hormone therapy (Grady et al., 1992a) after a review of literature since 1970 resulted in the conclusion that HT should probably be recommended for women who have had a hysterectomy and for those with coronary heart disease or at high risk for coronary heart disease. For other women, the authors could not recommend the best course (Grady et al., 1992b).

In the university clinics in Iowa, USA, HT use among women receiving care from gynaecologists was 2.6 times than among women receiving care from family practitioners, and current HT use rates between the clinics were similar (Levy et al., 2003). In Sweden 94% of women received their HT prescription from a gynaecologist (Thunell et al., 2005).

In Connecticut, USA, women aged 40-69 received a questionnaire of HT counselling. Women visiting both obstetrician-gynaecologist and family practitioner/internist were 3.1 times and those visiting only obstetrician-gynaecologist 2.5 times likely to have consulted about HT as those seeing only a family practitioner/internist (Gallagher et al., 2001b). Primary care practitioners more often than other

specialities have previously been found to counsel on prevention, in particular on weight, smoking, alcohol, and exercise (Andersson et al., 1998; Frank et al., 1995), with gynaecologists ranking HT as more important than counselling about smoking cessation (Andersson et al., 1998; Saver et al., 1997).

In the Newton et al. (2001) study in the USA about HT, prescribing frequency was not associated with the view that a strong scientific case has been made for HT in osteoporosis prevention (Newton et al., 2001) whereas in Belgium, prevention of osteoporosis increased prescription rate (Rozenberg et al., 1997a). In Finland and Sweden, risk factors for osteoporosis were regarded as an absolute or relative indication for HT by all of the GPs and gynaecologists, (Andersson et al., 1998; Hemminki et al., 1993c) but GPs more often considered it difficult to evaluate the advantages and disadvantages of HT than gynaecologists (Andersson et al., 1998; Hemminki et al., 1993c). In Finland gynaecologists recommended HT more often than women requested (Topo et al., 1993) and for a longer time than women wanted (Hemminki et al., 1995).

GPs and gynaecologists were unanimous that HT alleviates vasomotor symptoms and prevented osteoporosis but gynaecologists mentioned that HT could prevent wrinkles and might be effective against depression (Andersson et al., 1998). GPs more often than gynaecologists considered a history of venous thrombo-embolism an absolute contraindication for HT than gynaecologists (Andersson et al., 1998). In 1996 current ischaemic heart disease was regarded as an indication for HT by 43% of GPs and 60% of gynaecologists whereas 32% of the GPs and 26% of the gynaecologists thought this was an absolute or relative contraindication (Andersson et al., 1998).

2.4 Process in clinical trials

In the mid-1990s , two independent initiatives to improve the quality of reporting of randomised controlled trials led to the publication of the CONSORT (Consolidated Standards of Reporting Trials) statement, which was developed by an international group of clinical trialists, statisticians, epidemiologists, and biomedical editors (Begg et al., 1996). The consort statement concentrates on internal validity but it does not give any recommendation on reporting external validity. Drug trials are complex interventions and their processes have not been reported.

Long-term trials on HT characterize prevention, both primary and secondary prevention. Participants in secondary prevention HT trials have had a disease at some stage, for instance myocardial infarction (Kanaya et al., 2003), or breast cancer (Holmberg et al., 2004). Women in the primary prevention trials are defined as healthy (WHI) in spite of previous diagnosed chronic disease if the disease is in a latent stage e.g. hypertension.

2.4.1 Primary prevention trials on HT

Participants in the primary prevention trial are "healthy" participants, they do not have a previously diagnosed disease under research and the intervention is intended to prevent the disease. The length of the prevention trial was defined as 6 months in this review.

The first primary prevention trial on HT was a 3-year trial, the Postmenopausal Oestrogen/Progestin Interventions (PEPI) Trial to study oestrogen effect on blood lipid levels (The Writing Group for the PEPI Trial, 1995). It recruited 875 women between 1989–1991, and showed that oestrogen on its own has a beneficial effect on blood lipid levels but it should not be given to women with a uterus because of the proliferation of endometrium.

Primary prevention trials on HT have been conducted only rarely, the most notable being the WHI, Women's Health Initiative trial (The Women's Health Initiative Study Group, 1998), which started to recruit women in 1992 (n=16 608 in the oestrogen-progestin trial, and n= 10 739 in the oestrogen alone trial), but exposure was stopped prematurely because it showed increased risks for HT users. The WHI result was that oestrogen, combined with progestines or alone, does not prevent cardiovascular diseases (Writing Group for the Women's Health Initiative Investigators, 2002).

To study the effect of HT on bone mineral density, the Combination Treatment with Oestrogen and Calcitriol in the Prevention of Age-Related Bone Loss (STOP IT) was established (Gallagher et al., 2001a). The trial showed that hormone therapy/oestrogen therapy alone and in combination with calcitriol therapy was highly effective in reducing bone resorption and increasing bone mineral density at the hip and other clinically relevant sites in a group of women aged 65–77 years, compared with normal bone density for their age.

The Women's Intervention Study of Long Duration Oestrogen after Menopause (WISDOM) trial in the UK was to study HT long-term effects but it was stopped in 2002 before it had even closed the recruitment phase. The WISDOM trial used the same regimen as the WHI trial and the prematurely exposure stopping of the WHI made the WISDOM trial review their own situation. Many study questions in the WISDOM trial remained unanswered but the financer concluded that the required minimum of ten years to acquire answers was too expensive, and the trial was stopped (Vickers et al., 2002).

2.4.2 Secondary prevention trials on HT

Eligible participants in the secondary prevention trial are only those who have a diagnosed disease under research and the intervention is to prevent relapse. To find out relevant secondary prevention trials reviews were screened (Barrett-Connor

et al., 2001; Bath et al., 2005; Hemminki and McPherson, 1997a; Hemminki et al., 2000; Humphrey et al., 2002; LeBlanc, 2001; Miller et al., 2002; Nelson, 2004; Nelson et al., 2002; Salpeter et al., 2004; Torgerson et al., 2001b, 2001a; Torgerson et al., 1996; Yaffe et al., 1998). The reviews included both experimental and non-experimental studies. Trials were screened but no reports of the trial process were found. The reviews showed no other beneficial effects of HT except on bone mineral density, and harms seem to exceed this preventive effect. The quality of studies was varying.

The effect of HT on cardiovascular diseases has been studied. Hemminki and McPherson (Hemminki and McPherson, 1997a; Hemminki and McPherson, 2000) studied HT effect on cardiovascular diseases using meta-analysis and found that clinical trials do not support a beneficial effect of HT on cardiovascular diseases. Bath and Gray's (Bath and Gray, 2005) meta-analysis studied RCTs on the effect of HT on strokes. They found that HT was associated with an increased risk of stroke, particularly of the ischemic type. Among subjects who had a stroke, those taking HT seemed to have a worse outcome. HT cannot be recommended for the primary or secondary prevention of stroke. Miller et al.'s (Miller et al., 2002) systematic review studied HT effect on the risk of venous thromboembolism. Their conclusion was that postmenopausal oestrogen therapy is associated with an increased risk for venous thromboembolism, and this risk may be highest in the first year of use. Humphrey et al.'s (Humphrey et al., 2002) meta-analysis was on primary prevention of cardiovascular diseases and included both experimental and non-experimental studies, and resulted in the conclusion that their adjusted meta-analysis is consistent with recent randomized trials that have shown no benefit in the secondary or primary prevention of CVD events.

Nelson et al.'s (Nelson et al., 2002) review consisted both of observational studies and clinical trials and showed that benefits of HT include prevention of osteoporotic fractures and colorectal cancer, while prevention of dementia is uncertain. Harms include CHD, stroke, thromboembolic events, breast cancer with 5 or more years of use, and cholecystitis. In 2001 Barrett-Connor and Stuenkel (Barrett-Connor and Stuenkel, 2001) argued that while they were awaiting the results of the WHI and WISDOM trials that it seemed prudent to confine the use of HT to 1) symptomatic women; 2) oophorectomized women up to age 50–55, the usual age of menopause, and 3) for prevention or treatment of osteoporosis for the first 5 years after menopause. The five-year duration appears to carry no increased risk of breast cancer. Alternative proven therapies should be chosen for long-term prevention. Torgerson and Bell-Syer (Torgerson and Bell-Syer, 2001b, 2001a) found in their meta-analyses of RCTs a reduction in nonvertebral fractures in younger women, under 60 years, and showed a significant reduction in vertebral fractures associated with HT use.

LeBlanc et al. (LeBlanc, 2001) used RCTs and cohort studies in a review of the effect of HT on cognition. Their study showed specific cognitive effects but most studies had important methodological limitations. Yaffe et al. (Yaffe et al., 1998) also reviewed studies on the effect of HT on cognitive function and dementia; Their study also included both experimental and non-experimental studies. They did not recommend HT for prevention or treatment of Alzheimer disease or other dementias before adequate trials have been completed.

Salpeter et al. (Salpeter et al., 2004) studied mortality associated with HT in younger and older women and found that HT reduced total mortality in trials involving women with a mean age of under 60 years. No change in mortality was seen in trials involving women with mean age over 60 years.

2.4.3 Process in clinical trials

Previous studies of the process of preventive trials have mainly concerned the recruitment process (Oakley, 1992; Oakley et al., 1990; Oakley et al., 2003), the non-medical intervention effect on compliance (Campbell et al., 2001; Moore et al., 2002) and failures in recruitment (Amir et al., 2004) or randomization (Lumley et al., 1985). Oakley et al. (1990) and Oakley (1992, 2004) have reported a trial process on social support in motherhood and on peer-led sex education. They found that an evaluation of the intervention was integral to understanding the outcomes (Oakley, 1992; Oakley et al., 1990; Oakley et al., 2004).

De Zulueta (2001) has previously highlighted ethical issues concerning difficulties in obtaining valid consent in randomized controlled trials (RCT), and the choice of treatment for HIV infected pregnant mothers. Amir et al. (Amir et al., 2004) have described a failed recruitment for a nipple infection treatment trial, where a pilot study might have revealed weaknesses in the trial plan. In a trial on delivery for very low birth weight infants, Lumley et al.(Lumley et al., 1985) failed to achieve randomisation because of a critical shift in obstetric practice, while in Finland the pilot for a non-blind, patient-managed trial on hormone therapy (HT) revealed several obstacles for a main trial, including a possibly unwelcome return for the participant of vasomotor symptoms if HT use was discontinued, and also negative attitudes among Finnish physicians towards the trial (Hokkanen et al., 1997).

3 Aims of the study

The general aim of the study is to investigate the feasibility of the trial in respect of preference and to describe the research process in a changing environment of a preventive trial on postmenopausal hormone therapy (HT).

The specific aims of this study were:

1. to investigate women's perceptions of the climacteric and their preferences for hormone therapy (Article I)
2. to study Estonian physicians' perceptions of the climacteric and their preferences for hormone therapy (Article II)
3. to compare women's and physicians' perceptions of the climacteric and preference for hormone therapy (Articles I and II)
4. to compare characteristics of interested and non-interested women participating in the trial (Article III)
5. to study the effect of the trial design (blind vs. non-blind) on participation (Article IV)
6. to analyse changes in the research environment during the trial (Article V)

4 Material and methods

Various data from different sources have been used in the trial to answer the study aims (Figure 4.1) and have been collected at different times within the whole trial process (Figure 4.2). The data have been described separately, as well as a short description of the EPHT trial (more thorough description in the Appendix 1)

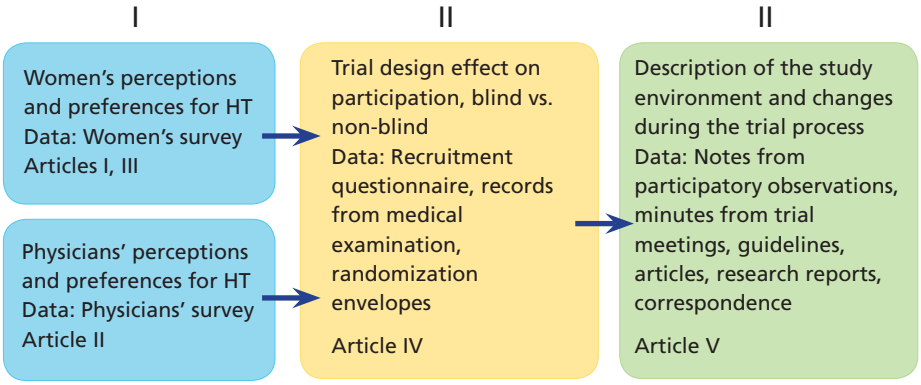

FIGURE 4.1 Main steps and data in the study process

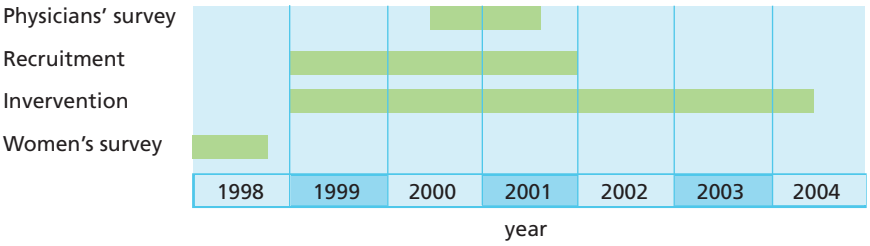

FIGURE 4.2 Time schedule of the data collection

4.1 Women's preferences

The women's population-based survey data came from the pilot study in 1998 for the Estonian Postmenopausal Hormone Therapy (EPHT) trial. The trial participants were recruited using postal questionnaires. The first portion (n=2000) of questionnaires were referred to and used as a "pilot questionnaire" for the whole trial (Appendix 2A), and it was wider than the subsequent recruitment questionnaires in providing more information of the respondents. The "recruitment questionnaire" is given in the Appendix 2B.

An anonymous postal questionnaire together with an invitation to join and a short description of the trial (Appendix 3) was sent in 1998 to a random sample of 2000 Estonian-speaking women aged 45–64 living in the capital area of Tallinn and the surrounding region, Harjumaa, and in the city of Tartu and surrounding region. (Age refers to that in January 1998). Women's names and addresses were drawn from the Population Registry. After two reminders the response rate was 69% (n=1312).

Most questions had previously been used in a Finnish survey in 1989 (Topo, 1997b); For the current survey we used both congruent and modified questions and the questionnaire was translated from Finnish to Estonian by Estonian researchers and back to Finnish by an Estonian translator with good Finnish skills. The Estonian questionnaire was first tested by some research colleagues at EKMI (TAI since the first of May, 2003) and then in a pilot of eight Estonian lay women aged between 45–64 to make sure that the content was understandable and relevant. The questionnaire included questions of the women's background characteristics, health status, menstruation, weight and height, health habits, health services utilisation, experiences and conceptions of the climacteric, and related symptoms and their management, (Appendix 2A). The questionnaire was divided into two parts: the first was meant for all, the second only to women whose menstrual periods had ceased or who used or who had used HT.

The statistical significance between the groups was determined using chi-squared-test and the two-tailed t-test of the proportions. In Article III, testing of the statistical significance of medians was done using a Mann-Whitney's U test. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated by logistic regression. SAS 8.0 was used in the analyses. For the purpose of the analyses, women were classified into four age-groups: 45–49, 50–54, 55–59 and 60–64 years. When comparing age-groups, the 50–54 age group were used as the reference on the assumption that menopause occurs most frequently in this age group. The data have been analysed in Articles I, II and III.

Open-ended questions about positive and negative features in the climacteric were analysed using a content analysis method. At the first step each word expressing experience about the climacteric was coded. At the second step, expressions

were reviewed and the categories formed. At the third step coded expressions were allocated to the categories, and finally, the frequencies of expressions in each category were calculated (Mayring, 2000).

The mean age of the respondents was 53.9 years, mean age at the cessation of menstrual periods was 49.8 years (SD 4.0), and there were no differences in the socioeconomic classes between the age-groups. Women lived mainly in urban or suburban areas.

4.2 Physicians' preferences

The Estonian physicians' survey. Data were collected using postal questionnaires to a random sample of gynaecologists and family practitioners in 2000. Combining physician lists of the Estonian Health Ministry, Gynaecological Society and Family Practice Society, we obtained a list of 726 gynaecologists and family practitioners (later called General Practitioner, GP). After the exclusion of 30 physicians without proper addresses, the names were organised in alphabetical order and numbered. The random number procedure in Excel was used to create a random sample of 500 physicians (212 gynaecologists and 288 GPs). The questionnaires were anonymous, and the respondents were asked to send their name tags in a separate envelope to avoid receiving a reminder. All physicians received a questionnaire in Estonian mentioning the availability of a Russian version on request; five physicians asked for this. After two reminders, 342 (68%) had responded. Following the exclusion of 21 questionnaires that had not been filled in (=physicians defining themselves as not part of the target population), 321 (155 gynaecologists and 166 GPs) remained. The distribution of respondents by speciality and sex corresponded well to the sample; we do not know the distribution of other background characteristics in the sample (Karttunen 2000).

Questionnaires included questions on current patient load, prescribing frequency of HT, benefits and harms of HT, and to whom HT should be prescribed and for how long. In the questionnaire, HT was first defined as hormone therapy used during the "climacteric" and afterwards referred to by the local lay expression. The questionnaire included explanations of "climacteric" and "postclimacteric". The literal translation of postmenopausal hormone therapy was "postclimacteric hormone therapy" in Finnish and "preventive hormone replacement therapy" in Estonian.

The questions used in this study were similar in the two surveys. The Finnish questions had been tested and used previously (Hemminki et al., 1993c). The Finnish questions were translated into Estonian by a native Estonian translator, the content was reviewed by two Estonian gynaecologists, and completing the questionnaires was tested by four Estonian physicians. The Russian questionnaire was

translated from the Estonian questionnaire in a translation office by a native Estonian translator with good Russian skills. The Estonian physicians' survey data has been analysed in Articles I and II.

Gynaecologists and GPs were compared to each other within the countries, and the two countries were compared within the specialties. Adjustments for age, workplace, and gender was made by logistic regression. Testing the statistical significance of the differences was done by a t-test, Chi-squared test and odds ratios (OR) with 95% confidence intervals.

4.3 The EPHT trial

The EPHT trial is an international project with Finnish and Estonian researchers, conducted in Estonia, a country of about 1.5 million inhabitants, in the Baltic region. The main co-ordinating of the trial was done in Finland. The author of this summary (SLH) acted as a co-ordinating investigator in the trial, starting at the time of the first financing applications for the trial in 1995. This early involvement in the trial provided me with a good position to follow the trial: its planning, recruitment, intervention and closing.

Estonia was considered as a possible environment for a new HT trial at the same time as the Women's International Study of long Duration Oestrogen after the Menopause (WISDOM) trial in the UK was under preparation and was looking for partners in Europe. After discussions we came to a co-operation agreement and the WISDOM trial applied financing from the EU in 1996 whilst including the EPHT trial as a partner. However, that application was not successful. But it was agreed in partnership with the WISDOM trial that we could obtain donated drugs for our trial from a drug company called Wyeth via the WISDOM trial. Other resources for the trial came from the Academy of Finland, the Ministry of Education in Finland, STAKES, and EKMI (known as TAI since the 1st of May, 2003). The study protocol was first approved by the Committees of Medical Ethics in Tampere, Finland in 1996 and later in Tallinn, Estonia in 1998 before the pilot study had begun.

It was decided to situate the study clinics in Tartu University Women's clinic, a tertiary care clinic, and in the Tallinn secondary care clinic, the East Central Hospital (previously Central Hospital) and West Central Hospitals (previously Pelgulinna Hospital). The clinics were chosen because of their situation and the research team members' previous contacts with these hospitals. Physicians were recruited among those already working in the clinics and who had an interest in working in the trial.

The names, personal identification numbers and addresses of all 39 713 women living in two Estonian regions of Harju and Tartu—including Tallinn, the capital of Estonia—and aged 50–64 in March 1999 (in the pilot study, aged 45–64

as of in February 1998) were obtained from the Estonian Population Registry. In the invitation letter women received information about the trial (Appendix 3) and a recruitment questionnaire (Appendix 2B). The questionnaire included questions about willingness to join a 5-year randomised trial and health status, including possible contraindications to joining the study and the date of their last period.

A total of 4295 women who were preliminary judged to be eligible according to the questionnaire data and who were interested in joining the trial were randomly assigned to one of the four study arms using random permuted blocks with a size of 16 each (Randomisation, see Appendix 1). The treatment allocation was enclosed in a non-transparent sealed envelope with a woman's group, study number and name on it and sent to the clinic that the woman had stated as being their preference in the recruitment questionnaire. There were four study arms: 1) blind drug arm; 2) blind placebo arm; 3) non-blind drug arm and 4) non-blind control arm (Figure 1 in Appendix 1). The randomly assigned women were mailed an invitation to a doctor's appointment. The invitation letter revealed only whether the woman was prerandomised to the blind or to the non-blind group. Trained trial physicians (eight gynaecologists at three clinical centres) conducted a thorough medical examination, including questioning about reproductive and health history, risk factors for CHD, and medication use, as well as measurement of blood pressure, examination of breasts, pelvic examination, Pap-smear for all women, and transvaginal sonography for women in the treatment arms (Inclusion and exclusion criteria see Table 3 in Appendix 1).

Of the 4295 prerandomized women, 1823 proved to be eligible and still wanted to join and so signed the informed consent, and their randomisation envelope was opened. Recruitment lasted from January 1999 to December 2001.

As the trial was originally planned to be part of WISDOM to add power to observations on disease outcomes, no sample size calculations were made for the long-term health outcomes. The sample size was calculated only for the short-term outcomes: changes in health-related quality of life and for the changes in the use of health services.

Pilot study

The feasibility of the study design was tested during the pilot study in 1998, which took place before the main trial in the same clinical centres. The women randomly selected for the pilot study had the same inclusion and exclusion criteria as women in the main trial, except that the lower age was 45 (50 in the main trial) at the time of sampling, and the time since the cessation of periods was 6 months (12 months in the main trial). The women recruited during the pilot study were included in the trial population, but in some analyses women under 50 years were excluded.

Intervention

After signing the informed consent the recruited woman was told by the trial physician to which group she had been randomly assigned. In the blind group, the women were told that they would be using either HT or a placebo; in the non-blind group, they were told that they would be receiving HT or no treatment. The drug in oral daily use in the treatment arms contained 0.625 mg of conjugated oestrogens (CEE) and 2.5 mg of medroxyprogesterone acetate (MPA) (or matched placebo in the placebo arm). In addition, women within 3 years of their last period received daily 2.5 mg of oral MPA in drug arms (or matched placebo in the placebo arm) to reduce the risk of bleeding. The drug bottles had a unique bottle number; in the non-blind arm the label contained information about the composition of the drug. The trial staff remained blinded until the end of the trial as regards the drug allocation in the blind group. Study participants were asked to fetch their drug bottles every 7 months after recruitment (in the pilot study, the second drug bottle was fetched 3 months after recruitment), and were invited to annual clinical examinations by means of mailed letters. The midwives had calling hours for all women in the trial in order to answer their questions.

4.4 Other data

Sales statistics of HT were obtained from the Agency of Medicines both in Estonia and in Finland. HT use was defined in daily defined doses (DDD). A DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO collaborating centre for drug statistics methodology, 2005). The calculations are based on the volume of sales to pharmacies and hospitals by wholesalers and on the assumed average dose per day for the drug. A figure of, for example,. 12 DDD/1 000 inhabitants/day indicates how many people per 1000 members of the population may in theory have received that standard dose of the drug. Drugs in ATC (Anatomical Therapeutic Chemical) classes G03C (oestrogens) and G03F (combined progestines and oestrogens) were used. The defined daily dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use.

The data for the study "impact of blinding on recruitment" comes from the recruitment process of the EPHT trial in 1999–2001 and from the one-year follow-up questionnaire. The trial is described in more detailed in Appendix 1. A recruitment questionnaire (n=37 713) was mailed to all women in the sample except the pilot women. This was shorter than the questionnaire for the 2000 women in the pilot survey.

By means of the recruitment questionnaire, demographic data for the women were collected, as well as health information for screening all potentially eligible women to participate in the trial. Randomisation envelopes with a woman's name and study number on were used to follow the recruitment process. The envelopes were stored at the clinics where the women would go for their recruitment examination. The trial physicians recorded results from the examination to the outpatient record and information from the recruitment examination was recorded on the recruitment form.

When a woman was not recruited, the clinic's midwives wrote the reason on the woman's envelope. After the recruitment period was completed, the envelopes were returned to TAI where the information from the envelopes was recorded. An opened and empty envelope indicated that a woman had been recruited to the trial. In cases where the envelope was opened but the recruitment material remained inside, there had been a mistake. Unopened envelopes indicated that a woman had not been recruited either because she had not come to the examination or she had been found to be ineligible, or she had changed her mind about participating during the examination. The reason for the ineligibility was written on the unopened envelope.

In the first year, women were asked in a questionnaire about their health and their feelings concerning the trial. For Article IV, data from the first seven recruitment rounds were used. In the blind group, 73% responded; in the non-blind group, the figure was 72%.

In Article V, other material was used. The data was drawn from written material 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. Observations were recorded in the notes from the discussions and reports from the visits. Letters were mainly emails from various partners during the trial years, mostly from Estonia from the persons involved in the trial, but also from the persons in the WISDOM trial in the UK and in Wyeth in the USA.

The author of this summary (SLH) has been involved with the trial since 1995 and worked as the co-ordinating trial investigator, beginning with the EPHT pilot study in 1997. SLH has systematically made notes and filed correspondence during the trial process. As a trial co-ordinator, SLH has been responsible for the randomisation and the recruitment process, organising the trial drugs from the WISDOM trial and their allocation to the recruited women (until that task was transferred to the TAI research assistant in 2001). SLH regularly visited the trial clinics and discussed with the trial staff.

5 Results and comments

In 1998 Estonia was favourable ground for a randomised controlled trial on HT because of low use of HT. In Estonia at the time of the pilot survey in 1998, only 3% of women aged 45-64 reported current HT use, and 10% ever use.

5.1 Women's perceptions of the climacteric and preference for HT (Article I)

The majority of the trial women were living in an urban area, they had a long general education and they were employed outside the home. Less than a third of the women had experienced vasomotor symptoms. Women were not familiar with HT and they did not have opinions about it, most of them could not take a stand on its health benefits. Women did not have strong feelings about the climacteric or HT; almost a fifth of women reported positive features in the climacteric and about a fourth reported negative features.

Women had obtained information on the climacteric most often from the media (55% of women). A third had received information from friends or relatives, and a quarter from a gynaecologist. A fifth of women had discussed the climacteric with their husband or partner, 36% with friends and 21% with relatives, but 39% of the women had not discussed it with anybody.

About 70% of the women gave their responses on the statements concerning the climacteric; the rest could not choose (about 13%) or did not answer (about 18%). About half of the women considered the climacteric a normal phase in a woman's life and said that it does not need treatment by a physician, and that a woman does not lose her femininity during the climacteric. Women who had reported hot flushes and sweating or who had wanted HT or used it, more often disagreed with the statement that a woman does not lose her femininity during the climacteric.

Women stated both positive and negative features in the climacteric. Almost a fifth reported the climacteric as positive because the cessation of menstrual periods made them free of irregular bleeding, and a quarter of the responding women were relieved because they did not have to fear becoming pregnant any more. Negative

features in the climacteric were reported by 28% of the women. Of them a bit more than a quarter mentioned the start of ageing, and a fifth hot flashes and sweating as negative features. Often women who reported negative features connected the climacteric with health problems like tiredness and deteriorated vision.

About half of the women could not decide their opinion on HT and a quarter gave no answer (Table 5.1.1). The statement that HT prevents osteoporosis was most difficult, and only 17% of the women expressed an opinion, 12% agreed. Educated women were more certain in their opinions about the climacteric and HT preventing osteoporosis (i.e. less often chose options "cannot say" or left unanswered).

On the statement about prescribing HT to all women showing climacteric symptoms, 37% of women gave an opinion: one half of them agreed and the other half disagreed. When stating that HT should be prescribed to all postmenopausal women, only 6% of the women agreed and a quarter disagreed.

No difference between the age-groups were found; the more education a woman had the more negative her opinion was on prescribing HT to all symptomatic women or to all postmenopausal women. Women who had used any drugs, who had visited health care several times within the past 12 months, or who had wanted to use or had used HT, agreed more often than other women with the statements that HT prevents osteoporosis, that HT should be prescribed to all women with menopausal symptoms and that HT should be prescribed to all postmenopausal women.

TABLE 5.1.1 Women's perceptions of hormone therapy by age-group (%)

	Age-group				
	45–49	50–54	55–59	60–64	All
	(n) 350	(n) 315	(n) 379	(n) 268	(n) 1312
HT prevents osteoporosis					
agree[1]	12	13	12	13	12
disagree[2]	6	5	5	3	5
HT to all symptomatic women					
agree[1]	20	20	17	14	18
disagree[2]	22	20	18	15	19
HT to all postmenopausal women					
agree[1]	7	7	4	6	6
disagree[2]	25	26	27	23	25

[1] includes "agree" and "nearly agree"
[2] includes "disagree" and "nearly disagree"

Comments: In Estonia like in other low HT use countries women were not familiar with HT or had opinions about it, and could not take a stand on its health benefits (Manzoli et al., 2004; Rachon et al., 2004). Awareness about the climacteric and hormone treatment seems to correlate to the use of HT (Akong et al., 2001; Lomranz et al., 2000; Sogaard et al., 2000), and that physicians' recommendations to use HT have influenced women (Lewin et al., 2003; MacLaren et al., 2001; Rozenberg et al., 1997; Sogaard et al., 2000; Topo et al., 1993). However, in Estonia education increased negative opinions about HT. In the studies from the late 1990s women with high education and the most awareness of oestrogen were more unwilling to use HT (Ekstrom et al., 2003; Lewin et al., 2003; Sogaard et al., 2000) (see (Hemminki, 2000).

In the Finnish survey in 1989, although 10 years older than the Estonian study, HT use was common and menopause and the climacteric had been widely discussed (Topo, 1997). It is possible that the public discussion had influenced women to have a more positive opinion of the climacteric, regardless of drug treatment. In Estonia in the 1990s, professional journals contained only a few articles about HT (Hemminki et al., 2004). We have no systematic data on what and how the climacteric and HT were discussed in media in Estonia.

5.2 Gynaecologists' and GPs' perceptions of the climacteric and preference for HT (Article II)

Physicians' perceptions on HT seemed to depend more on their speciality than their country or age and sex. Gynaecologists mentioned benefits of HT more often than GPs, and they were more in favour of longer treatment periods than GPs. Gynaecologists' favourable attitudes were approving of the trial.

A minority of physicians considered the climacteric as a normal phase that does not require treatment, GPs more often (15%) than gynaecologists (6%). Physicians had very favourable attitudes towards HT – gynaecologists more often than GPs (Table 5.2.1). Almost all respondents were of the opinion that HT contributes to the prevention of osteoporosis. Gynaecologists (87%) more often than GPs (76%) said that HT contributes to the prevention of cardiovascular diseases and to improved subjective well-being (86% and 67% respectively). About 80% of respondents said that a delay in ageing was one benefit. Adjustment for age, workplace, and gender did not notably change the differences between the specialties. GPs mentioned more harms for long-term HT than did gynaecologists. Both groups considered that harms included breast cancer (50%), uterine cancer (27–33%), and the return of menstruation (25–32%).

TABLE 5.2.1 Physicians opinions on the benefits and harms of combined postmenopausal oestrogen-progestin therapy, % of physicians giving affirmative answer, adjusted OR (95% confidence limits) between gynaecologists and GPs.

	Gyn % (n) 155	GP % (n) 166	OR	95% CI Adjusted[1]	
Benefits:					
Prevention of					
Osteoporosis	94	93	1.61	0.59	4.42
Cardiovascular disease	87	76	3.73	1.85	7.54
Breast cancer	6	11	0.40	0.16	0.97
Uterine cancer	21	15	1.45	0.79	2.68
Improved subj. well-being	86	67	3.74	2.02	6.91
Delay of ageing	79	82	0.72	0.39	1.31
Decreased weight problems	15	13	1.10	0.56	2.16
Harms:					
Increased risk of					
Cardiovascular disease	3	2	0.93	0.20	4.19
Breast cancer	50	51	1.15	0.71	1.87
Uterine cancer	27	33	0.76	0.45	1.27
Return of menstruation	25	32	0.65	0.39	1.11
Increased weight problems	21	30	0.62	0.36	1.08

[1] Adjusted for age, sex, and workplace; the reference is GP

Physicians' strong preference for HT became evident in their prescribing practices (Table 5.2.2). They believed in preventing chronic diseases. A large proportion of physicians stated that they would routinely prescribe HT for all women at menopause with no contraindication—regardless of symptoms; gynaecologists would recommend such use of HT more often (48%) than GPs (36%). After menopause more than a third of gynaecologists and less than a fifth of GPs favoured routine prescribing HT to all women without contraindication. No differences were found between the specialities in recommending HT to all women at risk of osteoporosis. GPs were more wary and more often recommended HT selectively than gynaecologists. The treatment lengths of those GPs who did prescribe HT were similar to those of gynaecologists: almost a fifth of gynaecologists and 18% of GPs recommended HT for a period of more than 10 years or for the rest of the woman's life. Gynaecologists were more favourable to long-term HT than GPs and they were convinced of HT benefits.

TABLE 5.2.2 Physicians' indications to prescribe HT, % of physicians.

	Gyn (n) 155	GP (n) 166
HT in postmenopausal phase		
For all women*	37	17
All at risk of osteoporosis	22	25
Individually at risk of osteoporosis	38	52
Only exceptionally	0	1
Other, no information	3	5
Total	100	100

* Without contraindication

Estonian women's and physicians' opinions about the climacteric and HT differed a lot, physicians had more preference for HT than women, and gynaecologists more than GPs. (Table 5.2.3). More than half of the women but a clear minority of physicians considered the climacteric as a normal phase. Physicians would more often recommend HT to women than woman would want.

Comments: Previous research suggests that physicians' positive attitude towards HT seems to increase prescribing (Andersson et al., 1998; Newton et al., 2001), and physicians tend to recommend HT more often than women want (Topo et al., 1993). Gynaecologists' own, or their spouses', use of HT reflects a preference for HT. HT use is higher among female gynaecologists and the spouses of physicians than among other women (Andersson et al., 1998; Isaacs et al., 1997; Nilsen et al., 2001). In the 10-year follow-up survey on women doctors' use of HT in the UK in 2003, uptake and continuation rates of HT have now declined, consistent with the prescription data, probably reflecting the changing nature of the evidence base. However, many women doctors still intended to continue long-term HT (Isaacs et al., 2005). In Estonia in 2000 (45% response rate), more than half of the responded

TABLE 5.2.3 Comparison of women's and Estonian physicians' opinions on the climacteric and HT, % [1]

	Women (n) 1312	GYN (n) 155	GP (n) 166
Normal phase of life, needs no HT	53	6***	15***
HT for all symptomatic women	18	48***	36***
HT for all postmenopausal women [2]	6	37***	17***

[1] Reference: women; *p<0.05; **p<0.01; ***p<0.001

[2] Without contraindication

female gynaecologists reported current or past use of HT. Almost all (95%) of the younger gynaecologists said that they will use HT (Wyeth Lederle 2000). In the USA, medical condition did not predict the duration of HT use among Medicaid recipients (Weiss et al., 2001). Obstetrician-gynaecologists were more likely than GPs and internists to report they believed in the preventive value of HT (Rolnick et al., 1999; Saver et al., 1997). Estonian gynaecologists more often than GPs considered drug advertising to be a factor contributing to increased HT use (Hemminki et al., 2004), while in the USA straight advertising did not have as much effect on prescribing as sponsored travel or education (Wazana, 2000).

Estonian physicians' attitudes were in many respects similar to Finnish physicians attitudes in spite of a ten-year time lag: Gynaecologists had a more positive attitude to HT than GPs, while a large proportion of physicians would have prescribed HT for all women at menopause regardless of symptoms (Hemminki et al., 1993a). In postmenopause more Estonian physicians favoured HT in spite of HERS study results about HT increasing the risk of various thromboembolisms in women with coronary heart disease (Grady et al., 2000). Gynaecologists more often than GPs routinely recommended HT to all, but Estonian physicians would recommend shorter periods of HT than GPs.

5.3 Characteristics of women interested and not interested in participating in the trial (Article III)

Of the approached 2000 pilot survey women, 11% were interested in joining the EPHT trial, this was 17% of respondents. And 42% of the respondents were "not interested" in participating, 40% "wanted more information" or "did not answer the question". The socioeconomic background characteristics of these four groups were very similar, but "non-interested" women were older than interested women as well as non-respondents (34%), and they were somewhat more often residents of the capital than were respondents.

In the case of many background characteristics, the interested and non-interested women were similar to each other, or the differences between them were small (Table 5.3.1). The major differences between them were in age, health, use of health services, perception on and attitude towards the menopause. When compared to non-interested respondents, interested women were younger, and they suffered from poorer health in terms of chronic diseases, more reported symptoms, and more visits to a physician. Interested women had more negative experiences with the menopause and a stronger preference for HT as a more positive attitude to HT and more often use of HT than had non-interested women.

TABLE 5.3.1. Differences in body mass index (BMI), symptoms, opinions on ageing and climacteric, and health services utilization between women interested and non-interested in participating the EPHT trial, %

	Interested % (n) 225	Non-interested % (n) 553	OR	(95% CI)[1]	
BMI >=30 kg/m^2	26	21	0.68	0.47	0.99
Depression	26	19	0.65	0.45	0.96
Sleeplessness	26	20	0.67	0.46	0.97
No symptoms	2	9	4.04	1.57	10.44
HT prevents osteoporosis[2]	27	9	4.27	2.75	6.64
HT to all women with symptoms[2]	32	12	3.20	2.16	4.74
HT to all postmenopausal women[2]	17	3	5.88	3.18	10.88
Physician visit in past year	76	68	1.53	1.06	2.20
Gynaecologist visit in past year	53	39	1.40	1.01	1.94
Used PHT at some time [3]	26	11	2.62	1.58	4.35
Used PHT at some time [4]	16	8	2.05	1.26	3.35

[1] Reference group: "interested"

[2] Missing values excluded from the denominator. The proportion of missing values varied from 17 to 21% in the "interested" group, and from 23 to 26% in the "non-interested" group.

[3] Excluding missing values, interested n=90 (40%), non-interested n=143 (26%), see Methods

[4] Including missing values in the denominator

Interested women's negative perceptions of the climacteric and positive attitude to HT, as well as a positive attitude towards HT on the part of gynecologists (Article II), may have influenced women's interest in the HT trial. By contrast, a fifth of the respondents had no opinion concerning HT. Its use is still infrequent in Estonia, and knowledge of HT is likely to have been scant. Interested women disagreed more often that the menopause is a normal phase, and gave more negative aspects of the climacteric than did non-interested women. They also held a more favourable opinion of HT than non-interested respondents.

Women's reasons for joining the trial, given retrospectively one year later in the follow-up questionnaire, were relatively similar in the two study groups; and in the non-blind study group, the two arms also gave fairly similar reasons (Table 5.3.2). Of the alternatives provided, women chose reasons which benefited them personally as well as reasons which were 'good' in general. The most common reasons given were the opportunity to obtain the medical examination by the trial physician, and the facilitation of Estonian research. "Free drugs" was chosen only by a very

TABLE 5.3.2 Women's reasons for joining the trial as reported in the follow-up survey after one year, % (and 95% confidence intervals, CI)[1)]

	Blind	Non-blind		Difference between blind and non-blind	
	Total	HT	Control	95% CI	
	%	%	%		
	(n) 592	(n) 371	(n) 395		
Altruistic					
Facilitate research	38	39	36	-5.2	5.2
Help future women	17	21	19	-1.7	6.6
Egoistic					
Physician's examination	43	42	57***[2)]	1.4	1.2
Help in menopause	36	35	22***[2)]	2.6	12.6
Better health care	9	11	11	-1.1	5.4
Better access	5	5	6	-2.2	2.9
Free drugs	5	6	5	-1.9	2.8
Other	6	8	5	-2.3	2.9

[1)] Women could choose several alternatives. HT = hormone therapy. Reasons are compared between the blind and non-blind group, and within the non-blind group between the HT and control groups.

[2)] The difference between HT and Control arm in non-blind group is statistically significant, ***p< 0.001.

few respondents. In the non-blind group, the women in the control group chose the annual physicians' examination less often and help in the menopause more often than was the case with the women receiving HT (Article IV).

In the follow-up questionnaire one year after the recruitment, over half of the women reported that prior to the trial they had had a preference for a particular arm. In the blind group and in the PHT arm, it was usually the active drug treatment arm. In the no-therapy arm, more women reported they had wanted to end up in the non-treatment arm.

Comments: As in previous preventive trials, the interested women were younger than those who were not interested (Britton et al., 1999). But in contrast to Britton et al. (Britton et al., 1999), who found that interested women had a more healthy lifestyle, we did not find differences in health habits—except with regard to being overweight. Like in previous studies HT users had more visits to the gynaecologist than non-users (Ekstrom et al., 2003; Hemminki et al., 1993a; Hundrup et al., 2002; Levy et al., 2003; Mueller et al., 2002), while also in our trial the use of health services positively correlated with women's willingness to join this trial. It seems that women's contacts to health services may increase their willingness to join a trial; or the use of health services may result from their poorer health: interested women had more chronic diseases and more symptoms. Or women expected

some benefits from the trial. In an imaginary trial of HT, the advantages that the women expected from the treatment was more important than how the benefits were described (Wragg et al., 2000).

Women's satisfaction with the allocated arm reflects the fact that the experience of the first year had distorted pre-trial opinions. The finding that people tend to be happy with the treatment that they receive is in accordance with previous literature (Fitzpatrick, 1993; Hall et al., 1988, 1990).

5.4 The trial design (blind vs non-blind) effect participation decision-making (Article IV)

Figure 5.4.1 shows the recruitment into the trial. A total of 39 713 women were invited to join the trial. Overall, the proportion of women interested in joining the trial was relatively high, 17% of those to whom an invitation was sent and 44% of those responding, expressed interest. On the basis of the questionnaire data, one third of the 6605 women interested were judged ineligible, mainly on the basis of their health or because they had menstruated within the past 12 months. This left 4295 willing and eligible women (11% of the 39 713 women approached) to be prerandomized and invited to the recruitment examination.

Both women and physicians made decisions at different stages of the recruitment process. In the invitation letter to the examination, women were specified their study group, blind or non-blind. Fewer women in the blind group (51%) than in the non-blind group (60%) decided to come to the physician's examination. During the examination, physicians defined rather more women in the blind group as ineligible than in the non-blind group. And rather more women changed their minds and decided not to join the blind group compared to the non-blind group. In the non-blind group, the final recruitment rate was 30% higher than in the blind group.

Exclusions made by physicians during the initial examination were obtained from their study records. A total of 481 women were found ineligible during the recruitment examination, only 18% (n=86) of them were excluded with predetermined reasons. Other health problems were commonly recorded, and some had resulted, on the judgments of physicians, in exclusion. Between the two groups there were no major differences in the numbers of health reasons recorded. In the blind group, 41 women had ailments listed in the exclusion list; the figure for the non-blind group was 45.

Comments: As expected, more women decided to join the preventive randomised trial in the non-blind group than in the blind group where they were going to know, after inclusion, to which treatment arm they belonged. Most of this difference was explained by the women's own decisions; the varying exclusions by

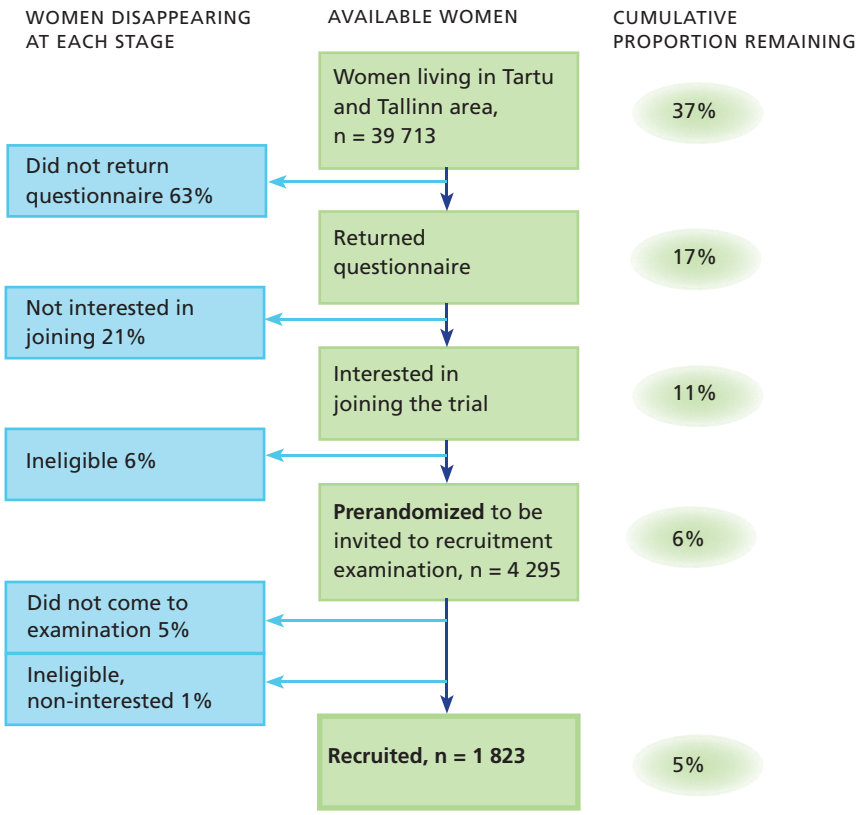

FIGURE 5.4.1 Schematic diagram illustrating effect of multiple stages of selection in the recruitment process of women into an RCT.

physicians explained less. This may reflect women's uncertainty connected to long-term preventive treatment with HT (Griffiths, 1999). It is easier to contemplate a long-term trial if informed of the treatment one will be receiving. This is especially true in the case of a treatment such as HT, which frequently may have immediate effects. Furthermore, women would be more willing to join a trial comparing two active drugs instead of trial comparing two active drugs and a placebo (Welton et al., 1999).

A review by Britton et al. (Britton et al., 1999) suggests that in treatment trials selective participation may exaggerate effects, while it may lead to underestimation in the case of prevention trials. Representative samples are possible in trials studying problems for which some treatment is needed or expected, and in which the informed consent is requested after inclusion in the study [see e.g. (Gallo et al., 1995; Hemminki et al., 1989; Zelen, 1979).

Estonian gynaecologists had a positive opinion of HT. We did not study the opinions of our study physicians but our impression is that their opinions were positive but they were worried about contraindications. The proportion of recruited women in the clinics varied from 45% to 41%. Exclusions over predefined ineligibility reasons may be due to the worry and they felt safer when including the women whose medication was known.

5.5 Analyses of changes in the research environment (Article V)

5.5.1 News from international HT studies

The EPHT trial had received its trial medication via WISDOM. Wyeth Aerst in the USA, a leading producer of HT medication globally, donated trial drugs to WISDOM, as well as to WHI. All three trials were using the same already licensed regimen. Using the same regimen would have been strong evidence if all the trials could have continued as planned. This did not happen, and exposure remained shorter than planned in all three trials.

In summer 2002, the WHI in the USA prematurely published results of the HT trial. It had stopped the intervention in the oestrogen-progestin study 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 (Writing Group for the Women's Health Initiative Investigators, 2002). Already in the middle of the EPHT recruitment period in 2000, and again in 2001, we had learnt that the participating women had been informed that the original hypothesis of cardiovascular protection was no longer likely, but the exposure continued because the balance of risks and benefits remained uncertain (Figure 5.5.1.1). The WISDOM trial in the UK, using the same trial medication as in the WHI, was stopped in October 2002 while it was still recruiting participants. The decision to stop the trial was based on a financial evaluation; at least ten more years would have been needed to get results from the trial (Vickers et al., 2002).

By summer 2003, the results of HT effects on dementia, cognitive functions, and quality of life in the WHI trial showed that HT is not safe for disease prevention and the Million Women Study results of HT effects on breast cancer supported the conclusions.

In spring 2003 the WHI trial for hysterectomised women with oestrogen alone or placebo treatment stopped exposure prematurely because the researches concluded that they had received all the necessary data and it did not show any benefit for prevention of coronary heart diseases (The Women's Health Initiative Steering Committee, 2004).

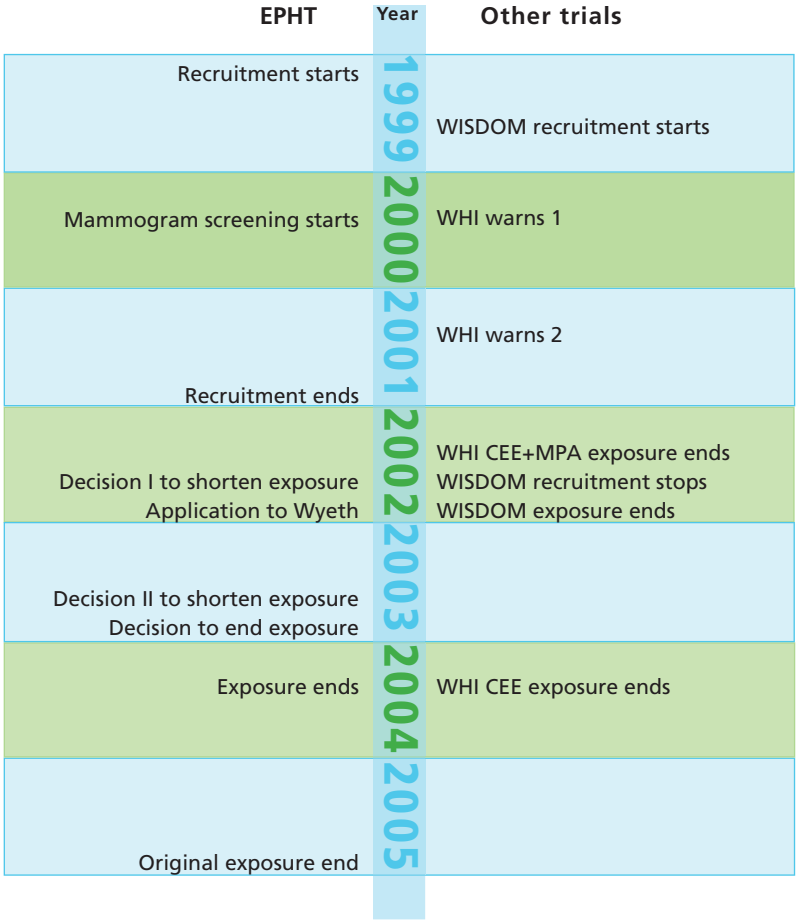

FIGURE 5.5.1.1 Time flow of the trial and parallel changes in the research environment

5.5.2 Changes in Estonian society and health care system

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, and in 2004 Estonia became a member of the European Union and its economic and scientific contacts with Western Europe increased. Various changes in legislation, relevant institutions, and financing occurred during our trial. The participating research institute, EKMI, was reorganized in 2003 and became the National Institute for Health Development (TAI), as well as reorganisations in the clinical centres in Tallinn: the Central hospital (currently East Tallinn central hospital) and Pelgulinna hospital (currently West Tallinn central hospital).

Changes were made to the data protection legislation that led to reduced access to various registries. The Data Protection Law was not clear in regard to the use of registries for research, and because of a rapid turnover of personnel in the ministries many were inexperienced in data protection issues. Disease outcome measures in the EPHT were planned according to the understanding of the regulations in Finland, which has a well-developed data protection practice. Because data collection for disease outcomes in our trial was mainly based on registries, new and changing regulations meant extra negotiations and time delays. Nevertheless, all necessary data other than deaths have been obtained up to the end of 2004 as planned.

Within the trial years, prices in Estonia went up, salaries rose, and new health technology emerged. Mammogram screening was not available in Estonia at the time of establishing the EPHT but came within a few years. This led us to add mammogram screening to our protocol—in addition to the advice given by local mammologists (Figure 5.5.1.1). Those women who were eligible for local mammogram mass-screening programs were encouraged to use them. For others we paid the costs, which were unexpectedly high.

A number of positive developments during the trial period involved improved communications and trial management: electronic mails replaced faxes, mobile phones use made contacting individuals easier and travelling between Finland and Estonia became notably faster.

5.5.3 Changes within the EPHT trial and related arrangements

The new information coming from other trials led to a lot of additional work: repeatedly we had to thoroughly analyse the information and consider its impact on our study protocol, and also to inform women and the clinical staff, as well as monitoring news reports.

In the EPHT trial we made three separate decisions to shorten the exposure. The first decision in December 2002 was based on the WHI decision to stop the intervention in the oestrogen- progestin study; we shortened the trial treatment time from the original five years for those women who had not yet been in the study for 4 years. The trial staff, physicians and midwives were informed by letter of the reasons why exposure in the WHI oestrogen- progestin study was stopped while all participating women were kept up to date with a semi-annual newsletter. Women were encouraged to contact the researcher if they wanted more information.

The second decision was in August 2003 after new reports from the WHI were published; in addition, the Million Women Study published its results (Million Women Study Collaborators, 2003). The exposure in the EPHT was shortened to three years for women who had by that time taken it for less than three years; those

in the 4th year of use continued until that year was completed. No other changes were made to the trial treatment practice but shortening of the exposure time.

The third decision came in December 2003 to stop the trial treatment gradually by May 31st 2004 to enable a final medical examination by the trial physicians for all trial women. This decision was based on our trial Data Monitoring Committee recommendation in their annual meeting as results from other trials were against the preventive use of HT. Results from the WHI oestrogen-alone study in spring 2004 (The Women's Health Initiative Steering Committee, 2004) had no effect on our trial because our decision to stop the exposure had already been taken, and the regimen in this trial was not identical with the EPHT trial drug.

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 made the annual interim analysis of the data and found no results that would have demanded a ceasing of the trial treatment. However, the only link for obtaining trial drugs had disappeared. Later on it was found that because of the shortening of the treatment time, the EPHT did not need any more drugs than had already been received. Furthermore, the plan had been to provide some data to WISDOM to strengthen their study power.

Comments:

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 is easily compromised through purchase of the drug outside the study. This was not a major issue in the EPHT trial though, as only some women receiving the placebo and less than 10% in the no-therapy arm had been subsequently prescribed HT (Vorobjov et al., 2005). But in the event that the early halting of WISDOM would have left the EPHT without trial medication, it would have been available in the pharmacies also for the trial purposes.

Exposure in the EPHT trial was stopped earlier than planned but the time was sufficiently long to provide data relevant to the research questions. Taking into account all the changes occurring in the research environment, the trial was successful. However, the low adherence (Vorobjov et al., 2005) and the relatively short exposure time reduced the power of the study (Veerus et al. 2006, in press). 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 burden of making changes to the protocol is extensive. Our trial was a small-scale trial which meant that it was easier to manage in the face of such constantly changing circumstances: the organising was flexible,

with both participants in the decision-making board and the clinics fully committed to the trial.

During the trial some unexpected expenses occurred and prices increased much faster than could have been expected at the time of planning. Financing a long-term trial is demanding because budgets are often made on current prices. Furthermore, in the Finnish financing system, funding decisions usually cover only a couple of years at a time, making changes difficult and adding uncertainty to the planning. Public funding is crucial in maintaining the independence of the trial from commercial biases.

Preventive drug trials are by nature long-term trials because the disease outcomes usually require long exposure or long follow-up to be detectable and usually need large numbers of participants, thus increasing the costs involved (The ATCB cancer prevention study group, 1994; The Women's Health Initiative Study Group, 1998). Even publicly funded researchers usually ask for drugs to be donated from drug companies. Pharmaceutical companies are not 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 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 willing to take the risk. In 2001 Wyeth covered 70% of the global HT market (Clark, 2003). 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 (Buist et al., 2004; Hersh et al., 2004; Hillman et al., 2004).

In the EPHT trial, all the trial clinics were located in Estonia, but the main scientific co-ordination was in Finland. Health care was different between the two countries, although Estonia was adopting more and more western practices. Many external changes placed additional demands especially on the local co-ordinator, who had to seek new solutions and contacts. The small degree of financial resources did not make things easier. Having constant contact with the study clinics was extremely important. Practices in the clinic changed and midwifes had their clinical duties in addition to our trial. An experienced eye in clinical work was needed to trace changes that often happened without an explicit plan.

6 Discussion

Estonia was a suitable country to conduct a long-term clinical trial. The low rate of HT use offered a good possibility for randomisation, women did not have such preferences for HT that would have prevented the randomisation, and easy access to health care services made the trial safer for women. Physicians' strong preference for HT was positive for the trial because they might have considered the trial a good means to increase HT preventive use in Estonia. The intervention with a licensed trial medication made the ethical burden less, and long-term treatment more acceptable. Furthermore, the timing of the trial was successful. Doubts about the HT effect on preventing chronic diseases had emerged and trials on the effect of HT long-term use were needed.

The environment was favourable to the trial. Estonian primary health care is provided by independent family doctors and the women had good access to health care. Good health registers enabled covering outcome measures, although some problems in availability occurred. Currently health registries are available for research purposes.

Response rates in the two surveys were good to average, offering representative information on both women's and physicians' perceptions of the climacteric and preferences for HT.

6.1 Methodological considerations

Randomization is the most effective method of controlling individual extraneous variables. The primarily function of randomization is to secure comparable groups, that is, to equalize the groups with respect to extraneous variables. A distinct advantage of random assignment, compared with other methods of controlling extraneous variables, is that randomization controls all possible sources of extraneous variation, without any conscious decision on the researcher's part about which variables need to be controlled.

Results of the EPHT trial can be generalized to Caucasian middle-aged women. Our trial population was a cohort of 50–64-year-old women living in Tallinn and Tartu and in the surrounding regions. The inclusion criteria in the trial were large.

There were only two steps where exclusion criteria were used, first on the basis of response data and finally at the recruitment examination. During the recruitment examination more women were excluded than predefined reasons necessitated. Physicians used their own clinical judgement, and more women were excluded in the blind group. Anyway, we succeeded in recruiting 5% of the population and that is a good average.

During our recruitment process we have not systematically collected information of those who did not participate in the EPHT. Our pilot study suggests that women who entered the trial were younger and used more health care services than those who did not join the trial. We have responses from women who did not want to join but at the recruitment stage we did not emphasize to women that we were interested both in those who want to participate and those who don't; 63% of women did not respond to the recruitment questionnaire. Anyway, in our pilot study 19% wanted to join or wanted more information before deciding, these two groups were similar in many respects. In the trial 17% of the women approached showed interest in joining.

The trial was set up to follow the local treatment practice, and all the study physicians were working as clinicians in the study centres. Recruited women received their treatment in the public health care system but they also had a possibility to use study physicians between the scheduled annual examinations. As this study on the research process shows, in spite of the many changes in the environment during the trial years, including the shortening of trial exposure, no other such changes were made that would have affected the intervention.

To study recruitment from the beginning, women should have been pre-randomised already at the stage of the first invitation, but already at the planning stage it was found to be unfeasible with the available recourses. Randomisation after exclusion of potentially ineligible women on the basis of questionnaire information and before inviting women to the examination was early enough to offer women a possibility to consider whether to join or not, and to investigate their preference for the blind or non-blind design. Using a non-blind group, especially in long-term trials was encouraging. Although more women were recruited to the non-blind group, the pre-randomisation was successful and there was no basic difference between the study groups. Whether it had an effect on outcomes is not yet known. The reports of other EPHT trial outcomes will be available at http://www.stakes.fi/palvelut/kay/projektit/hormoni.htm ->publications/ as soon as they have been published.

Outcome measurements for diseases could be obtained through registries, so it did not need extra data collection and health data for all participants could be obtained. But, use of the registries also proved to be a limitation because of the changes in the data protection law that restricted the linkage. It may also limit obtaining long-term outcomes in the future.

Two surveys were used in this trial to study women's and physicians' preferences for HT. Preferences were measured indirectly using physicians' recommendations for HT use as an indication for preference, and correspondingly women's wish to use HT for prevention purposes. We succeeded in obtaining fairly good response rates and it improves the generalizability of the study results. Women's survey data provided information about participating and non-participating women. Both groups were similar to women who did or did not use HT in western countries as to age, education, health services use and preferences for HT.

6.2 Women's and physicians' preferences for HT

The low use of HT in Estonia can be seen a positive feature for a trial purpose. It allowed a representative sample of non-exposed postmenopausal women to be randomised. They had scant knowledge about HT and they did not have strong prejudice of HT and can be assumed that they follow randomisation instructions, on the contrary than in Finland where women's strong attitude proved to be an obstacle to the randomisation (Hokkanen et al., 1997).

The majority of the trial women were living in an urban area, had a high general education and were employed outside home, these were all features that predicted HT use in a Finnish study in 1989 (Topo, 1997), as well as in studies in other countries (Brett et al., 2003; Finley et al., 2001; Friedman-Koss et al., 2002; Keating et al., 1999; Levy et al., 2003; Li et al., 2000; Mueller et al., 2002; Thunell et al., 2005). We could expect Estonian women to be adherent to the trial treatment, although we now know that only half of the recruited women did follow the recommendation in the trial arms. This reminds us that adherence parallels a real life situation for HT use in Western countries (Vorobjov et al., 2005).

As found elsewhere, HT users visited gynaecologists more often than non-users (Ekstrom et al., 2003; Hundrup et al., 2002; Mueller et al., 2002). In Sweden 94% of women received their HT prescription from a gynaecologist (Thunell et al., 2005). This suggests the importance of gynaecologists' professional influence in the diffusion of HT.

The use of HT is low in Estonia. At the time of a survey in 2000, Estonian physicians' positive attitudes may have pointed to an increasing use of HT. The discrepancy between Estonian physicians' opinions and the low level of use showed that opinions could have pre-dated higher use by many years. In Finland, a similar relationship was found between opinions in 1989 and an increase in use in the 1990s. Nevertheless, HT use in Estonia has not increased as could have been expected; on the contrary, it has declined (State Agency of Medicines 2005). Results from recent studies (Writing Group for the Women's Health Initiative Investigators, 2002) (Anderson et al., 2004) (Beral et al., 2003) may have affected prescriptions.

There is a lapse of eleven years between the surveys for physicians in Finland in 1989 (Hemminki et al., 1993b) and Estonia in 2000, but physicians' opinions are very similar in both countries. At the time of the Finnish survey, the assumed cardioprotective effects of oestrogens were based on observational studies suggesting a risk reduction among HT users (Stampfer et al., 1991) (Grady et al., 1992). Observational data had also supported HT benefits for bone mineral density (Weiss et al., 1980) (Ettinger et al., 1985). Randomised controlled trials on HT were lacking at that time. Between the two surveys of 1989 and 2000, one large secondary prevention randomised controlled trial on postmenopausal hormone therapy, The Heart and Oestrogen/progestin Replacement Study (HERS), was completed. Its conclusion was that HT increases the risk of venous thromboembolism in women with coronary heart disease (Grady et al., 2000). Its results cannot be seen in the Estonian study: most Estonian physicians and more so than in Finland believed that HT contributes towards the prevention of cardiovascular diseases. The first guidelines for HT in Estonia were published in 2001, some months after our survey. Indications for preventive purposes included: the risk of cardiovascular diseases, including problems caused by smoking; and a cardiovascular disease in the case of a close relative (Karro et al. 2001). In their new guidelines in December 2002, indications includes, in addition to vasomotor symptoms and vaginal dryness, for example mental symptoms like sleep disturbances and affective syndrome. For prevention only, osteoporosis and osteopenia have been mentioned (ENS, 2002).

In Estonia gynaecologists had a stronger preference for HT than did GPs. After Estonia gained independence from the Soviet Union at the beginning of the 1990s, the prescribing of HT was in practice left to gynaecologists . Compared to Finland, however, no such practice has applied, and this situation is an unlikely explanation for strong preference. The same difference could be found between specialties in many countries (Andersson et al., 1998; Baron et al., 1998; Exline et al., 1998; Hemminki et al., 1993b; Nilsen et al., 2001; Norman et al., 1994; Rolnick et al., 1999; Thomson et al., 2001). Rather, professional interests and promotion activities may have been important (Frank et al., 2003). Gynaecologists in Estonia have been the main target for postgraduate education on HT conducted by the drug industry (Hemminki et al., 2004).

According to current trials (Writing Group for the Women's Health Initiative Investigators, 2002) (Veerus et al. 2006 in press), it can be assumed that long-term HT will be promoted as an important indication for the prevention of osteoporosis. And because Estonian gynaecologists and GPs unanimously agree with regard to this benefit, the indication is likely to remain. On the other hand, results from randomised clinical trials show that HT increases the incidence of breast cancer, cardiovascular events and stroke. But in addition to preventing fractures, it decreases the rate of colorectal cancer (Barrett-Connor et al., 2001) (Beral et al., 2002; Writing Group for the Women's Health Initiative Investigators, 2002). On the ot-

her hand, results from recent randomised trials show that HT, at least combined oestrogen-progestin regimens, increases the occurrence of various other diseases, including breast cancer and cardiovascular events (Barrett-Connor and Stuenkel, 2001) (Beral et al., 2002; Writing Group for the Women's Health Initiative Investigators, 2002). Among older women, HT did not improve the health-related quality of life or other psychosocial outcomes (Hays et al., 2003). HT increased the risk of probable dementia and did not prevent mild cognitive impairment (Shumaker et al., 2003), but increased the risk of clinically meaningful cognitive decline (Rapp et al., 2003). The recent results from randomised clinical trials have changed prescribing practices in many countries and the use of HT declined already in 2002 in many countries, in Estonia even before that time and it has stayed low (State Agency of Medicines, 2005). However, in many countries HT use has begun to rise again.

6.3 Decision-making at recruitment

During the recruitment process the whole population in Tartu and Tallinn and the surrounding regions had a possibility to be recruited, although it is not known how representative the recruited women are. We cannot say for sure whether women were seeking more treatment than prevention, but a comparison between women interested and not interested in joining the trial suggests that this may be the case. In the recruitment examination, physicians defined rather more women in the blind group as ineligible, and rather more women decided not to join the trial in the blind than in the non-blind group. In the non-blind group, the final recruitment rate was 30% higher than in the blind group. We do not know the preferences of the study physicians but the proportions of recruited women by the clinics were similar, from 45% to 41%. Compared to the women in the WHI trial (Writing Group for the Women's Health Initiative Investigators, 2002), the Estonian women are healthier and younger.

Ellenberg (Ellenberg, 1994) argues that information involving the selection process should be obtained at each stage of selection, beginning with the screening of potential participants and proceeding to the final enrolment of those who agree to take part. The Estonian legislation did not allow a linkage of non-participants to the general data sources so as enable an evaluation of the effects on participants, in other words whether there was a potential bias. The EPHT recruitment process may establish some basis for judging limits when generalising results of an intervention trial although the characteristics of persons who did not return the questionnaire remain largely unknown. At the trial planning stage it was decided not to send any reminders at the first recruitment stage when women were invited to participate, and the response rate stayed at 37%.

Women preferred a non-blind study over a blind study. We could assume that it is easier to contemplate a long-term trial when the treatment is known. In a British study investigating, in a hypothetical situation, the feasibility of doing a trial with hormone therapy, rather more women said they would be willing to join a trial comparing two active drugs than a trial comparing two active drugs and a placebo (Welton et al., 1999). In the same way we may hypothesize that when physicians were in doubt concerning the eligibility of a woman, they may have felt safer about including the woman when they knew that the medication would be known.

The influence on numbers is important in terms of feasibility (many trials suffer from fewer patients than expected) (Rolnick et al., 2001; Ross et al., 1999; Ruffin et al., 2000). In this trial, non-blinding was useful in increasing the total number of women in the study. One may hypothesize that the higher the participation rate is, the better the participants represent the target population. In this study, in both groups only a proportion of women who were approached and were eligible joined the trial. Thus, allowing subjects to know their treatment (after trial inclusion) did not improve the generalisability to our target population, that is mid-aged healthy Estonian women.

6.4 Changing research environment

Simultaneous trials on HT in other countries made running the EPHT trial challenging. The halting of the WISDOM trial during the EPHT recruitment phase was a threat but in the end did not negatively effect the EPHT trial, except that the possibility to increase the study power was missed. From the beginning it had been planned to provide disease outcomes to WISDOM but that opportunity was missed.

Changes in the Estonian society were more rapid than we could have ever expected. Health care was under reconstruction but organizational changes in health care did not directly affect the EPHT; the clinical centers remained the same but the burden in their economy needed more negotiations. More demanding were the changes in the data protection legislation and its interpretations. A different result in this process might have destroyed our possibilities to obtain disease outcome data through health registers.

Results from other international trials forced us to make changes in our trial protocol, and necessitated a lot of extra work to keep both trial staff and participating women informed about the newly evolving information on HT effects and to keep management of the EPHT trial updated and capable of running the trial. We did not notice any negative effect of the new information on trial adherence in spite of the somewhat alarming results. The trial Steering Group was informed, and it was able to make the necessary decisions to continue the exposure. The role of the Data Monitoring Committee in a situation where the continued exposure is under consideration is crucial—How to provide information and keep the Committee updated on new trial results?

7 Conclusions

It was possible to establish a long-term preventive, randomised controlled trial of HT in Estonia using a licensed drug. HT use in the country was low although the medication had been available for some years. Women had not formed an opinion of HT and strong preference either to HT or the placebo arm was missing; this made the randomisation possible. Low income hindered HT use outside the study. Physicians, especially gynaecologists, had strong preference for HT. For them the trial was a way of increasing a therapy they considered useful.

Research results from other trials (WHI oestrogen/progestin trial) had a notable effect on our trial: it led to shortening of the trial treatment and lessened our efforts to increase treatment adherence, and removed the possibility of pooling the disease outcomes with the WISDOM trial because that had ceased. The EPHT results can be pooled to other trials on HT. A small-scale trial with flexibility and motivated researchers helped in keeping the trial going on. During our trial, Estonian society and health care changed rapidly, but these changes did not violate the results, although some made obtaining trial disease outcomes difficult.

More women decided to participate in the non-blind study than the blind study. Using non-blind design in long-term preventive trials may bring more participants, but also possibilities for more contamination, a lowering of the costs, and make running the trial easier. More research is needed on non-blind trial designs on trial feasibility and on the effects on results.

The results of the trial can be generalized to Caucasian middle-aged women. According to a survey prior to recruitment, women who wanted to participate to the trial were probably looking rather more often for treatment than for prevention, they reported more often chronic diseases and symptoms than those women who did not want to join the trial.

It was planned that the trial protocol follows Estonian practice on HT treatment as much as possible. Changes in the society were very rapid; nevertheless, reorganizations in the health care system did not have an effect on women's access to health care or on the treatment they received.

Planning a long-term trial is demanding. Currently it can be expected that society changes quickly and even unexpectedly. Thus, already at the planning stage some flexibility should be built into the project. Sufficient financing from inde-

pendent sources is needed. Trial methodology should be developed, with the non-blind study design offering a valuable addition to randomised designs.

The aim of this thesis was not to study the long-term effects of HT. The results of other studies in the EPHT trial will be available at the trial web sites at http://www.stakes.fi/palvelut/kay/projektit/hormoni.htm ->publications/ as soon as they have been published.

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Appendix 1

Description of the Estonian postmenopausal hormone therapy (EPHT) trial

The EPHT trial is a four-arm randomized controlled preventive trial, consisting of a blind and a non-blind sub-trial. The blind study represents a traditional randomized, double-blind, placebo-controlled trial except for the early randomization prior to informed consent, whereas, the non-blind study is a non-conventional randomized controlled trial with an open-label female hormone therapy (HT) arm and a non-treatment arm (Figure 1). The aim of the trial was to find out both long-term and short-term effects of (HT) on postmenopausal women; the long-term (5 years) were effects on the risk of cancers, heart and cardiovascular diseases and bone fractures and metabolic diseases. Short term outcomes were immediate effects on well-being and symptoms, effects on the experience of the climacteric and on ageing and on partner relationships, as well as effects on the use of health services. The methodological outcomes were the placebo and trial effect by means of the design, as well as the further effects of these on recruitment and compliance.

The recruitment period lasted from January 1999 to December 2001. Trial treatment was stopped gradually from January 2004 to the 31st of May 2004.

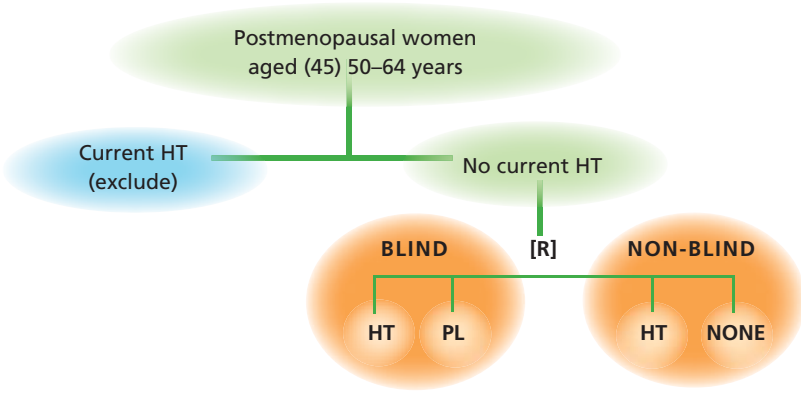

FIGURE 1. The EPHT trial design

Participants

Participants in the EPHT trial were 1823 postmenopausal women. For the feasibility study a sample of 2000 women, aged 45–64 years, was picked from the Estonian Population Registry in 1998. Based on experiences gained in the feasibility study the age range was changed to 50–64 years. For the rest of the sample in 1999, the age limit of 50–64 was used. The mean age at recruitment was 58.2 years and the mean age at menopause was 50.2 years. Women's baseline characteristics are given in the Table 1.

Eligible women had had their last menstruation at least six months previous to the pilot study, and 12 months previously for the rest of the participants; they had also had no current HT use in the last six months. Conditions leading to exclusion are presented in the Table 2.

TABLE 1. Baseline characteristics of the women in the four trial arms

	Blind HT n=415	Placebo n=381	Non-blind HT n=503	Control n=524	Total n=1823
Mean age in years at recruitment, (S.D.)	58 (4)	59 (4)	59 (4)	59 (4)	
Mean age in years at menopause, (S.D.)	50 (4)	50 (4)	50 (4)	51 (4)	
Mean BMI, (S.D.)	27 (5)	27 (4)	27 (5)	27 (5)	
Educational level, %					
Primary school	11	11	9	12	
Secondary school	56	58	56	56	
University	33	31	35	32	
Married/cohabiting, %	62	60	64	62	
Hysterectomies, %	11	13	14	14	
Oral contraceptives, never used, %	85	89	87	92	
Smoking, currently, %	16	14	13	17	

The data comes from recruitment questionnaires. Abbreviations: HT, postmenopausal hormone therapy; S.D. standard deviation; BMI, body mass index (kg/m^2).

TABLE 2. The Estonian Postmenopausal Hormone Therapy trial inclusion and exclusion criteria

Inclusion criteria

- age of 45–64 years in the first pilot sample (n=2000), and 50–64 in the second sample in January 1999 (n=37 713).
- Estonian nationality and Estonian speaking
- woman had sickness insurance because visit costs to the clinics were compensated from the sickness insurance.

Exclusion criteria.

Women were excluded from the study who had the following characteristics and health problems, as reported by women themselves or reported in patient records or health registers or were found during the clinical examination:

- current HT in last six months
- menstrual period within the last 12 months, in pilot I it was 6 months
- untreated endometrial adenomatosis or atypical hyperplasia of endometrium. (In the last recruitment year, since 14.5.2001 ultrasound was no longer carried out within recruitment examination)
- breast cancer, endometrial cancer, ovarian cancer
- any cancer treated less than 5 years ago
- history of meningioma
- myocardial infarction within the last 6 months
- history of hepatitis (not hepatitis A) or liver functional disorders during last 3 months
- history of deep vein thrombosis, pulmonary embolism, cerebral infarction
- porphyria
- hypertension of more than 170/110 mmHg in spite of medication
- endometriosis

After the recruitment of women to pilot I, women were excluded who have used:

- SERM medication (Tamoxifen®, Toremifen®, Noremifen®, Raloxifen®).

Randomization

Because one of the aims in the EPHT trial was to find out whether blinding has any effect on recruitment, the randomization of the women to the four trial arms had to be done before women were invited to the recruitment examination. We used postal questionnaires to contact the potential participating women (N=39 713). Screening the responses of 14 892 women, we were able to identify 4295 interested and potentially eligible women for randomization. For the 2311 women interested in participating but not eligible, we mailed a thank-you letter and gave the reason for ineligibility.

The trial was mainly co-ordinated in Finland and the randomization was done at the National Research and Development Centre for Welfare and Health

(STAKES). The data of the interested and potentially eligible women was cleaned of the personal identification number before e-mailing them to the co-ordinator as it is prohibited to submit personal information from Estonia to another country. Only study code numbers were used in the randomization process. Women were randomized by three trial centers into four treatment arms (Figure 1): a blind active treatment arm, a blind placebo arm, a non-blind active arm and a non-blind control arm, using a computer-based block randomization program (block size 16). The arms formed blind and non-blind groups. The randomizations were made in nine rounds between November 1998 and June 2001 (Table 3). To ensure blinding during the recruitment process completely opaque envelopes were used. After randomization the medication sheet and the information letter were sealed into an envelope with a woman's group and study code number on. The medication sheet included the woman's study number, group and the number of the first drug bottle. In the trial treatment arms the enclosed letter asked the woman 1) to take medication, 2) visit the study physician annually, 3) fill the annual questionnaire, the Breast Examination card and Health Status Card, as well as 4) giving the duration of the trial, 5) giving information about possible unexpected effects, 6) to inform the about discontinuation of the tablets in an annual questionnaire, and the reason

TABLE 3. Recruitment time-table

Questionnaires sent			Randomisation		Invitation	Recruitment				
							Blind		Non-blind	
Lot	Time	Number	Time	N	Time (month/year)	Total	HT	Pl	HT	Contr
Pilot Study (+2 reminders)	3/1998 (5/98, 10/98)	2 000	15.11.1998	125	1–2/1999	45	11	8	9	17
Lot 1	23.3.1999	2 000	24.4.1999	212	4–5/1999	115	26	25	30	34
Lot 2	9.8.1999	6 000	10.9.1999	547	10/1999	244	51	55	69	69
Lot 3	6.9.1999	6 000	28.10.1999	583	12/1999 –1/2000	267	63	57	65	82
Lot 4	3.1.2000	6 000	11.2.2000	761	2–3/2000	348	81	77	103	87
Lot 5	17.2.2000	6 000	30.3.2000	656	P,T 4–5/2000; K8–9/2000	275	65	54	74	82
Lot 6	3.4.2000	6 000	6.6.2000	703	10–12 /2000	258	60	51	71	76
Lot 7	23.10.2000	5 713	9.1.2001	692	P,T 2–3/2001; K8-9/2001	265	56	52	81	76
Lot 8			28.6.2001	16	9/2001	6	2	2	1	1
Total		39 713		4 295		1 823	415	381	503	524

*P=Tallinn East, K=Tallinn West, T=Tartu

for it, 7) and finally an instruction that in case of any other treatment, to inform the doctor about their participation in the HT trial. In the blind group women were further told that the clinical staff were unaware of their treatment arm.

In the non-blind group control arm the letter 1) asked women to complete the annual questionnaire, 2) advised them to participate biannually in the Pap-smear test, 3) told that they can visit the study physician if they want but they were not specifically invited, 4) asked them to use the Breast Examination Card and the Health Status Card and return them together with the annual questionnaire, 5) asked them to inform if starting HT as well as stopping the treatment in the annual questionnaire. The envelopes were transferred to the research institute in Tallinn, where woman's name were added to the envelope and then sent on to the clinic that she had chosen.

Screening

Recruitment began in January 1999 and ended in December 2001. The aim was to recruit 3000 women to the EPHT trial. Names and addresses of all Estonian and Estonian speaking women, aged 50–64 (aged 45 in the pilot), living in the capital area (Tallinn and Harju region), and in Tartu and the surrounding region, were picked from the Population Register. Three study clinics, two in the capital area in Tallinn and one in Tartu had been chosen. Women were recruited using postal questionnaires (n=39 713) with a letter inviting them to participate in the HT trial (Appendix 3).

Attached to the recruitment questionnaire was a two-page leaflet describing the need for the trial and the assumed and known beneficial and harmful effects of HT. The trial design was described in general terms, not mentioning the blind and non-blind group but saying that those interested will be randomly allocated into three groups (hormone therapy, drugs, no treatment). The questionnaire asked about women's health, background characteristics, their interest in joining the trial ("Do you want to participate in a trial on postmenopausal therapy as described in the enclosed leaflet?"), and which of the local clinics they would like to attend. The interested women found to be ineligible on the basis of the questionnaire data were sent a thank-you letter stating the reasons for their ineligibility.

Two different questionnaires were used. The first, called "the pilot questionnaire" (Appendix 2a), was sent to 2000 women aged 45–64 years. It consisted of 49 questions both to define women's eligibility for the trial and to provide information about women's opinions about the climacteric and HT. Two reminders were sent to non-respondents (response rate 69%). The pilot questionnaire asked about living area, education, working situation, occupation, family, health status and health habits, symptoms, diseases, medication, operations, menstruation, visits to a physician, climacteric and HT. Based on the first pilot it was decided to change the lower

age-limit to 50 years instead of 45 because so few women in the 45–49 age-group were postmenopausal, and the time after the last menstruation was changed from 6 months to 12 months to be classified as postmenopausal.

The second questionnaire, called "the recruitment questionnaire" Appendix 2b, was shorter than the pilot questionnaire. It was used to recruit women to the trial, and no reminders were used. The recruitment questionnaire included only questions which were important to the recruitment in defining the responder's eligibility for the trial. Women were asked about living area, education, working situation, marital status, health status, smoking, menstruation, symptoms, HT use within past 6 months. The first batch of 2000 recruitment questionnaires was used as a pilot study II, and no changes were made to the questionnaire or the study design after pilot study II.

The trial design was tested in these two pilot rounds and modified after the first pilot in 1999. The pilot women are included in the trial. The recruitment letters were mailed in eight batches, the first and the second (pilot I and pilot II) included 2000 questionnaires each, and the other five batches included some 6000 each (Table 3).

Recruitment

Altogether 14 892 women returned the questionnaire, of which 10 597 did not want to join or were found to be ineligible. The number of preliminary eligible women identified was 4295, and these women were randomized into four trial arms forming two groups, a blind group with active treatment (HT) and placebo (PL) arms, and a non-blind group with open-label hormone treatment (HT) and no treatment (NONE) in the control arm (Figure 1). After randomization women were invited to the recruitment examination. In the invitation letter they were told their group, blind or non-blind and asked to make an appointment for a physician's examination. The information letter was the same for the two groups except for the descriptions of the blind or non-blind groups. The existence of the other group was no longer mentioned. The letter was practically oriented, giving details on: 1) how to make the appointment, 2) what would happen during the examination, 3) informed consent procedure and data use by the researchers, 4) obtaining and using study drugs, 5) how follow-up would occur, and 6) what women should do, i.e., if they stopped taking their drugs (or started HT in the no-therapy arm of the non-blind group).

To make an appointment for a physician's clinical examination, the letter advised the woman to telephone a study midwife at the clinic. At each clinic, one or two service midwives were specially trained and their salary partly paid by the project. Besides reserving the time, the midwives provided further information on the trial, which many women requested. If the woman invited did not visit the

clinic, a co-ordinating study physician invited her by phone. Starting with the 3rd recruitment round, if the woman had not been reached by phone, a reminder letter was sent asking her to make an appointment. Before the trial started - and once during the recruitment (May 2000) – the researchers described the trial in local newspapers and on TV in order to increase women's awareness of the trial and interest in its purpose.

Women in the blind arm were told that they received either inactive or placebo therapy and that even their physician would not know which it was. Women in the non-blind group were told whether they had received hormone therapy or no treatment at all, and this is known both to the woman and to the physician.

Eligibility

The inclusion and exclusion criteria were first used to screen the potentially eligible women before randomization and these women were then invited to a recruitment examination, where women's eligibility was reconfirmed. They were interviewed, their breasts were palpated and a thorough gynaecological examination was performed. Inclusion and exclusion criteria are given in Table 2.

Baseline visits

When the woman arrived at the clinic, the examining physician (eight physicians) knew which group she was in (blind or non-blind), but not which arm. The physicians were employees of the clinics but were trained for the trial and paid according to the number of women examined. They were provided with examination protocols and they had been given detailed instructions on what to ask and measure, and what were the exclusion criteria (including current or previous breast or uterine cancer, any other cancer less than 5 years previously, history of deep vein thrombosis, pulmonary embolism, cerebral infarction, meningioma, porphyria, endometriosis, myocardial infarction less than 6 months previously, liver functional disorders or hepatitis less than 3 months previously, hypertension in spite of drug therapy, irregular postmenopausal bleeding, abnormal Pap-smear results, menstrual bleeding within the last 12 months, desire for HT, plans to move out of the area). Gynecological ultrasound examination was offered in the blind group to all women with uterus and/or ovaries intact, and in the non-blind group only to those women who were recruited to the HT arm. If a woman was found to be ineligible because of the ultrasound examination she would have been classified as non-adherent. In any case, gynaecologists wanted to offer a similar practice to all women and ultrasound was performed for most non-blind group women before they signed the informed consent.

TABLE 4. Data collection components of the EPHT trial

Procedure	Baseline V	Baseline Q	1st AV	1st Q	2nd AV	2nd Q	3rd AV	3rd Q	4th AV	4th Q
Informed consent	x									
Medication use	x	x	x	x	x	x	x	x	x	x
Pelvic examination	x		x		x		x		x	
Endometrium evaluation	x									
Physical examination	x		x		x		x		x	
Side effect evaluation	x		x	x	x	x	x	x	x	x
Quality of life, WHQ				x						
Quality of life, EuroQoL						x		x		x
Symptoms	x	x		x		x		x		
Pap-smear	x				x				x	
Weight		x		x		x		x		x
Mammogram screening (since2000)										

V = visit, Q = questionnaire, AV = annual visit

Determining eligibility required two visits to the clinic in the blind group and three in the non-blind, because results of some examinations were not ready at the first visit. (Table 4) After the physician found a woman eligible, her consent was requested (in writing), and the envelope containing the code for the treatment arm was opened; once the envelope was opened, the woman was included into the trial. (Table 5) The envelope contained a drug sheet for the midwife and a one-page leaflet to be given to the woman. This leaflet re-explained the study design and the method of taking or not taking the drug, describing potential adverse effects and any symptoms that necessitated contacting the study physician or an emergency clinic. The drug sheet contained the unique identification code for the drug bottle and technical information for the midwife, who stored the sheet for her use. Women in the HT arm of the non-blind group who had not yet received gynecological ultrasound scanning were offered it after opening the envelope. (Women who showed an abnormal result were retained in the trial, but drugs were not given to them.) Women were taught how to palpate their breasts to search for breast tumors.

During visits to the physician, some eligible women lost interest in the trial. If this occurred before the envelope was opened, the woman in question was excluded from the trial. If it occurred after the envelope was opened, she was included in the trial and followed through registers and annual questionnaires. The reasons for not recruiting were recorded on the randomization envelope, which was returned to the main co-ordinator.

TABLE 5. Quarterly progress of the recruitment

Recr.time	n	recruited/year (n)	yearly cumulative number. (n)
1.1.–31.3.1999	38		
1.4.–30.6.1999	89		
1.7.–30.9.1999	17		
1.10–31.12.1999	199		
1999		343	343
1.1.–31.3.2000	343		
1.4.–30.6.2000	266		
1.7.–30.9.2000	142		
1.10–31.12.2000	252		
2000		1003	1346
1.1.–31.3.2001	120		
1.4.–30.6.2001	157		
1.7.–30.9.2001	40		
1.10–31.12.2001	160		
2001		477	1823

Intervention

The drug used was Prempro® (Wyeth-Ayerst, Philadelphia, USA), a fixed combination of conjugated equine estrogens (CEE) 0.625 mg and medroxyprogesterone acetate (MPA), taken daily. The MPA dose was 5 mg for women whose last menstrual period had occurred less than three years previously, and 2.5 mg for the rest. Matched tablets were used in the blind group placebo arm.

In the non-blind group women who had been randomised to active treatment received the same regimen, which was described on the label of the drug bottle.

Those women with previous hysterectomy (n=4) who were recruited at the first pilot received CEE 0.625 mg or matched placebo. Women who were later hysterectomized were not classified separately and they received the same regimen as women with an intact uterus because it was not possible to distinguish if the hysterectomy had been total or not.

Blinding

Participants in the blind study, as well as staff at the clinical centres, were blinded to the treatment assignment. The individual treatment codes were known only to the main coordinator at STAKES. At randomization each woman was reserved a drug bottle with a unique identification number. The co-ordinator prepared a list

of allocated drug bottles, and the bottles were transported to the recruitment clinics together with the randomization envelopes. When a woman had received her drug bottle, information was sent to the research institute and also to the main coordinator to get the number of the next drug bottle. This practice continued until spring 2002 when the local research assistant began to allocate the drug bottles.

To prevent unblinding of clinical centre staff, all young postmenopausal women (last period less than 3 years previously) bleeding women received first extra progestin, or matched placebo. If bleeding continued ultrasound, endometrial biopsy, and treatment interruption were available interventions. Unblinding was not possible in any cases.

Intervention and follow-up

After signing the informed consent, it was confirmed to the recruited woman by the trial physician as to which group she had been randomly assigned. In the blind group, the women were told that they would be using either HT or a placebo; in the non-blind group, they were told that they would be receiving HT or no treatment. The drug in oral daily use in the treatment arms contained 0.625 mg of conjugated estrogens (CEE) and 2.5 mg of medroxyprogesterone acetate (MPA) (or matched placebo in the placebo arm). In addition, women within 3 years of their last period received 2.5 mg of oral MPA daily in the drug arms (or matched placebo in the placebo arm) to reduce the risk of bleeding. The drug bottles had a unique bottle number; in the non-blind arm the label contained information about the composition of the drug. The trial staff remained blinded until the end of the trial as regards the drug allocation in the blind group.

Study participants were asked to fetch their drug bottles every 7 months after recruitment (in the pilot study, the second drug bottle was picked up 3 months after recruitment), and were invited to annual clinical examinations by means of mailed letters. The letter included also a questionnaire, a breast examination card, MAMA Calendar (Gästrin 1994), and a health status follow-up card. By means of the questionnaires, we collected annual data about women's symptoms, health status, weight, health services use, and record of taking trial medication. The annual medical examination included measurement of weight and arterial blood pressure, a pelvic examination and breast inspection. A Pap-smear was taken every second year. Other examinations (endometrial histology, possible blood tests) were made only on clinical indications. Vaginal bleeding was managed by an algorithm that accounts for time and severity of bleeding, and sonographically determined endometrial thickness. No unblinding was performed during the trial. All women were trained to palpate their breasts monthly.

During the intervention phase of the trial, a follow-up was performed via annual visits to the study physician and through annual questionnaires. Annual

questionnaires asked about women's health status and their feelings concerning the trial, including trial treatment adherence; women in the blind group and HT women in the non-blind group were reminded to reserve an appointment for their annual physician's examination.

Annual follow-up visits to the clinics were scheduled for all other women, except those in the control arm of the non-blind study, to assess side effects and encourage adherence. Usually women received their next drug bottle at the same visit. Annual visits at the clinic repeated health, risk factor, and general examinations with gynecological examination and breast palpations. No blood tests were taken.

Ethical approval for the trial

All participants gave written informed consent. The trial protocol was approved by Tallinn Medical Research Ethics Committee, Estonia. Preliminary approval of the protocol had been obtained from the Ethical Committee of Pirkanmaa Hospital District, Tampere, Finland prior to applying for financing for the trial.

Data collection

Follow-up was done by annual linkages to the Estonian Cancer Registry, Estonian Mortality database, the database of the Estonian Health Insurance Fund that includes data about all provided health services. The linkages were made using personal identification number.

The unit of registration at the Health Insurance Fund is one disease episode, and the following data are recorded: dates of start and end of the episode, number of visits to the doctor or number of inpatient days in a hospital, diagnostic examinations, treatment procedures, surgical interventions, the cost of each service separately, up to three medical diagnoses as the cause for care according to the 10th revision of International Classification of Diseases and the date of death if relevant. For prescribed drugs, the following information is recorded: data about the physician and the patient, name and ATC-code of the drug, diagnosis according to International Classification, and date of writing the prescription.

Appendix 2a

HORM/PILOTTI2/1998

CLIMACTERIC AND WOMEN'S HEALTH

HOW TO ANSWER
Most of the questions include a given choice. Please, choose the one which best applies to you and circle the number of the answer. Where appropriate, use the empty space provided for your answer. Other questions will separate instructions.

BASIC INFORMATION OF YOU

1. Date of Birth: day _____ month _____ year _____

2. Nationality _____

3. Place of residence
1 Tallinn
2 Harju county
3 Tartu
4 Tartu county
5 Other ⇨ **3B. Where?** _____

4. Do you live?
1 In a town centre
2 Outside the town centre/in a suburban area
3 In a village
4 In the countryside outside of a village

5. What is your highest level of education?
1 Less than preliminary
2 Preliminary
3 Basic
4 Secondary
5 Vocational
6 Higher
7 Scientific degree
8 Other ⇨ **5B. What?** _____

6. Are you currently?

1 In a paid job
2 No, I am working at home
3 No, I am a disability pensioner (not employed)
4 No, I am a pensioner (not employed)
5 No, I am unemployed
6 Other ⇨ **6B. Specify** _____

7. What is or was your occupation/profession? _____

8. What is your current marital status?

1 Married or cohabitant
2 Single
3 Divorced ⇨ **8B. Since** _____
4 Separated ⇨ **8C. Since**_____
5 A widow ⇨ **8D. Since**_____

9. Have you given birth?

1 No
2 yes ⇨ **9B. Birth years of the girls**_____
⇨ **9C. Birth years of the boys**_____

10. Who lives in your household?

Encircle several alternatives if necessary..

1 I live alone
2 Husband or male partner
3 Daughters ⇨ **10B. Number** _____
4 Sons ⇨ **10C. Number** _____
5 Other relatives ⇨ **10D. Number** _____
6 Other persons ⇨ **10E. Number** _____

YOUR HEALTH

Next questions concern your health.

11. Height _____ cm

12. Weight _____ kg

13. What is your current health?

1 Good
2 Rather good
3 Moderate
4 Rather poor
5 Poor

14. How much do you exercise during your free-time?

1 Not at all
2 A little
3 A fair amount
4 Quite a lot
5 A lot

15. During the previous two weeks have you used calcium products (tablets etc.)?

1 Daily
2 Every now and then
3 Not at all

16. Do you currently smoke?

1 No
2 Yes, occasionally
3 Yes, daily ⇨ **16B. How many cigarettes a day? _____**

17. How much alcohol do you use?

1 A lot
2 Quite a lot
3 A reasonable amount
4 Rather little or little
5 Not at all

18. During the previous two weeks, have you had any of the following symptoms or problems?

If needed, you can use several choices.

1. Dizziness
2. Tiredness
3. Diarrhea or constipation
4. Irritability
5. Constant cough
6. Depression
7. Backache
8. Stomach pain
9. Headache
10. Sweating
11. Joint/muscle ache
12. Shortness of breath
13. Hot flashes
14. Sore throat
15. Sleeplessness
16. Loss of appetite
17. Menstrual problems
18. Fluid (water) retention
19. No symptoms

19. Have you had painful sexual intercourse within past two weeks

1 No
2 Yes
3 I have had no sexual intercourse

20. Have you had or currently have following diseases (symptoms)?

Circle correct answer to every disease or symptom.

		Yes, currently	Yes, previously	Never
1	Breast cancer	1	2	3
2	Endometrial cancer	1	2	3
3	Ovarian cancer	1	2	3
4	Myocardial infarction	1	2	3
5	Heart failure	1	2	3
6	Hypertension	1	2	3
	⇨ **20B. Hypertension in spite of medication** 1 Yes 2 No			
7	Brain infarction	1	2	3
8	Deep vein thrombosis	1	2	3
9	Pulmonary embolismt	1	2	3
10	Hepatitis or functional liver disorders	1	2	3
11	Kidney insufficiency	1	2	3
12	Diabetes	1	2	3
13	Itch during pregnancy, or icterus	1	2	3

21. Have you had or currently have some other chronic diseases (or symptoms) other than those mentioned above)?

1 No
2 Yes ⇨ **21B. What?** _____

22. Do you regularly use any medications?

1 No
2 Yes ⇨

	22B. Name of the drug	**22C. Reason for use**
1	_____	_____
2	_____	_____
3	_____	_____

23. Have you had any of the following operations

Please give year of operation. You may choose more than one alternative.

1 Hysterectomy ⇨ **23B. Year?** _____
2 Oophorectomy one side ⇨ **23C. Year?** _____
3 Oophorectomy both sides ⇨ **23D. Year?** _____
4 Breast cancer operation ⇨ **23E. Year?** _____
5 No operations mentioned above

MENSTRUATION AND VISITS TO A PHYSICIAN

24. When was your last period?

1 Less than 6 months ago
2 6 - 12 months ago
3 Over 12 months ago ⇨ **24B. How old were you?** _____ yrs.

25. Have you had irregular bleeding after your menstruation ceased?

1 No
2 Yes
3 I still have regular menstruation

26. The climacteric can be divided into three phases. Where are you now?

1 The climacteric is still to come
2 I am in the climacteric
3 The climacteric has past

27. During the last 12 months have you visited a physician (excluding a dentist)?

1 No
2 1-2 times
3 3 - 4 times
4 5 - 6 times
5 7 times or more

28. During the last 12 months have you visited a gynaecologist?

1 No
2 1-2 times
3 3 - 4 times
4 5 - 6 times
5 7 times or more

CLIMACTERIC AND HORMONE THERAPY

29. Have you visited a physician because of climacteric symptoms?
Choose several, if appropriate

1 Yes, I have visited a gynaecologist
2 Yes, I have visited another physician
3 No, I have not visited a physician, but I have considered it
4 No, I have not even considered visiting a physician
5 I have no climacteric problems

30. What were the climacteric problems that made you to visit a physician?

1 I have not visited a physician because of the climacteric
2 I visited ⇨ **30B. Why?** _____

31. Have you wanted to get hormone treatment because of climactric symptoms?

1 No
2 Yes ⇨ **31B. Why?** _____
3 I do not remember

32. Has a physician ever recommended hormone treatment to you because of climacteric symptoms?

1 No
2 Yes
3 I do not remember

33. Have you ever discussed the menopause with any of the following persons? Choose several, if appropriate.

1 Friends
2 Relatives
3 Husband/companion
4 Someone else ⇨ **33B. Who?**_____
5 With no one

34. Have you received information about the menopause from any of the following sources? Circle after every statement the number which corresponds best to your opinion

	I have got information from...	A lot	Some	None at all
1	gynaecology	1	2	3
2	other physician	1	2	3
3	midwife, nurse or physician's assistant	1	2	3
4	friends or relatives	1	2	3
5	newspapers, books, radio, television	1	2	3
6	other source	1	2	3

⇨ **34B. Specify?**_____

35. Have you received enough information about the climacteric?

1 Yes
2 No ⇨ **35B. What further information would you want?**

_____

36. In the following we give some statements about menopause and hormones (estrogens or estrogens combined with progestins) used during menopause and postmenopause.

In each case circle the alternative which best describes your opinion.

		Totally agree	Agree	Don't know	Somewhat disagree	Totally disagree
1	Hormones effectively prevent osteoporosis	1	2	3	4	5
2	Menopause is a normal phase in a woman's life and usually doesn't need a doctor's treatment	1	2	3	4	5
3	Hormones should be given to all middle-aged women having (climacteric) symptoms	1	2	3	4	5
4	A woman does not lose her femininity during climacteric	1	2	3	4	5
5	Hormones should be given to most postmenopausal women	1	2	3	4	5

37. What are the positive sides of the climacteric?

1 I find nothing positive in it
2 The positive is ⇨ **37B**._____
3 I cannot say

38. What are the negative sides of the climacteric?

1 I find nothing negative in it
2 The negative is ⇨ **38B**._____
3 I cannot say

The following questions are about the climacteric and hormone therapy (estrogen and combined preparations). Women with normal menstruation and those who do not use hormone therapy can stop here. Others we ask to continue filling in the questionnaire.

39. Have you had climacteric symptoms?

1 No.
2 Yes ⇨ **39B. What?** _____

40. Do/did menopause affect the frequency of sexual intercourse?

1 It has reduced in number
2 It has stayed similar
3 It has increased in number
4 I have not had intercourse for years before menopause
5 I have never had intercourse
6 I am not at menopause

41. Have you ever taken hormone medicine (estrogens or combined preparations as a pill, cream, injection, patch, gel or some other form) as a result of the climacteric?
Encircle several alternatives if necessary**?**

1 I have never used hormone therapy
2 I have used hormone therapy in the form of vaginal cream
3 I have used during the climacteric hormones such as pills, patches, gels etc .
4 I have used after the climacteric hormones such as pills, patches, gels etc .
5 I do not remember or I cannot say

42. Has your physician ever prescribed to you other medication in addition to hormones?

1 No
2 Yes ⇨ **42B. What?**
   1 Sleeping pills
   2 Tranquillizes
   3 Other ⇨ **42C. What?**_____
3 I do not remember

43. Has your physician prescribed medicines other than hormones as a result of climacteric?

If possible, write the name of the preparation. If needed, give several answers.

1 No

2 Yes ⇨ **43B. What?**

1 "Lady Life"

2 "Damjana"

3 Other ⇨ **43C. What?**_____

44. Have you treated climacteric symptoms in some other way that has not been mentioned earlier?

1 No

2 Yes ⇨ **44B. How?** _____

3 I am not yet in the climacteric

45. Have you used female hormone therapy?

1 No

2 Yes ⇨ **45B. When did you start?** in 19____ _____(month)

3 I do not remember

46. Why were you prescribed hormone therapy (Please, mention all the reasons)?

1 I received hormone treatment during the climacteric

⇨ **46B. Because?** _____

2 I received hormone treatment after the climacteric

⇨ **46C. Because?** _____

47. Have you stopped hormone treatment?

1 I have never taken hormone therapy

2 I am still taking hormone treatment

3 I stopped taking hormone treatment ⇨ **47B. When?** in 19____ _____(month)

48. Why did you stop hormone therapy?

If needed, please, give several answers.

1 Therapy was meant only for a certain period

2 I wanted to stop

⇨ **48B. Why?**_____

3 A physician advised me to stop

⇨ **48C. Why?**_____

4 Other reason

⇨ **48D. What?**_____ _____

49. Do You wish to participate in the hormone therapy trial described in the leaflet that is attached to the questionnaire?

1 Yes
2 No
3 I do not know before getting more information *

*More information can be obtained from Pelgulinna Women's Hospital from Dr. Piret Veerus or a midwife Eevi Beldsinskilt tel. (22) 496 504 on Thursday's at 10 –12 o'clock or by mail from:

Piret Veerus
Eksperimentaalse ja Kliinilise Meditsiini Instituut
Hiiu 42
Tallinn
EE 0016

MANY THANKS FOR FILLING IN THE QUESTIONNAIRE

IF YOU WANT TO CONTINUE TO PARTICIPATE, PLEASE WRITE YOUR CONTACT INFORMATION SO THAT WE CAN INVITE YOU TO A PHYSICIAN'S EXAMINATION. WOMEN LIVING IN TARTU OR TARTU COUNTY CAN VISIT THE WOMEN'S CLINIC OF THE UNIVERSITY OF TARTU.

WOMEN IN TALLINN: PLEASE CIRCLE WHETHER YOU WANT TO VISIT THE CENTRAL HOSPITAL'S WOMEN'S CLINIC OR PELGULINNA WOMEN'S HOSPITAL

1 CENTRAL HOSPITAL WOMEN'S CLINIC
2 PELGULINNA HOSPITAL WOMEN'S CLINIC

ADDRESS: _____

_____

_____

TELEPHONE._____

Appendix 2b

HORM.TRIAL1/1999

CLIMACTERIC AND WOMEN'S HEALTH

Study number __ __ __ __ __

Please answer all questions. Encircle the number of the most suitable answer or where appropriate, write your answer in the empty space provided.

1. Your place of residence

1 Tallinn
2 Harjumaa
3 Tartu
4 Tartumaa
5 Other

2. Your highest level of education

1 Preliminary
2 Basic
3 Secondary
4 Vocational
5 Higher
6 Scientific degree

3. Are you currently in work?

1 No, I am retired
2 No, I am a housewife
3 No, I am unemployed
4 Yes, I do

4. Your marital status

1 Single
2 Married, cohabiting
3 Divorced
4 Widow

5. Your date of birth: day ..... **month**..... **year**.....

6. Your nationality:.....

7. Your height: ..... cm

8. Your current weight..... kg

9. Do you have health insurance?

1 No
2 Yes

10. Have your menstrual periods ceased?

1 No, I am still menstruating
2 Yes, the last period was 6-12 months ago
3 Yes, the last period was more than 12 months ago

11. When was your last period? Year ..... month .....
3 I do not remember

12. Have you had any of the following symptoms <u>in last two weeks</u>?

	No	Yes	I do not remember
dizziness(1)	1	2	3
tiredness(2)	1	2	3
diarrhoea or constipation (3)	1	2	3
irritability (4)	1	2	3
constant cough(5)	1	2	3
depression(6)	1	2	3
backache (7)	1	2	3
stomach pain(8)	1	2	3
headache (9)	1	2	3
cold sweats (10)	1	2	3
joint/muscle ache(11)	1	2	3
shortness of breath (12)	1	2	3
hot flashes (13)	1	2	3
sore throat (14)	1	2	3
sleeplessness(15)	1	2	3
loss of appetite (16)	1	2	3
fluid (water) retention (17)	1	2	3
menstrual disorders (18)	1	2	3

13. Which of these above mentioned symptoms bother(ed) you (Write here the numbers of the symptoms above which bothered you)
.....……...

14. Did you use hormone therapy (estrogens or estrogens plus progestogens) in the last 6 months (excluding contraceptive pills)?

1 No
2 Yes
3 I do not know

15. The name of the hormone therapy regimen you used in past 6 months (either pills, injections, transdermal patches or gel)?

.....…….

3 I do not know

16. **Have you ever been diagnosed as having had**

	No	Yes	Diagnosed in year	month	I do not know
Myocardial infarction	1	2	.....	.....	3
Hepatitis or functional liver disorders	1	2	.....	.....	3

17. Has your doctor ever diagnosed you as having had

	No	Yes	I do not know
Brain infarction	1	2	3
Pulmonary embolismt	1	2	3
Deep vein thrombosis	1	2	3
Porphyria	1	2	3
Endometriosis	1	2	3

18. Have you ever had any of the following tumours?

	No	Yes	I do not know
Endometrial cancer	1	2	3
Ovarian cancer	1	2	3
Breast cancer	1	2	3
Cancer at any other site	1	2	3
Benign brain tumour (meningioom)	1	2	3

19. Have ýou had a hysterectomy?

1	No
2	Yes
3	I do not know

20. Has your mother, daughter or sister been diagnosed as having breast cancer?

	No	Yes	I do not know
Mother	1	2	3
Doughter	1	2	3
Sister	1	2	3

21. Do/did you smoke?

1	No
2	Yes, I smoke
3	Yes, I did earlier

22. Do you wish to participate in the hormone therapy trial described in the leaflet that is attached to the questionnaire?

1 No
2 Yes, my contact data is the following :

Name.....

Address.....

.....

phone at home..... at work.....

If you have any questions related to the participation in the trial, please contact Dr Mare Tekkel by phone 514334 on workdays from 9 to 12 a.m.

23. If you wish to participate in the trial and live in Tallinn or Harju region, do you prefer to join the trial at

1 Central Hospital, Women's clinic
2 Pelgulinna Women's Hospital
3 I do not have any preferences

If you are eligible for participation, we will try to take your preference into consideration. Women from Tartu and Tartu County can join the trial at Tartu University Women's Clinic.

Date of filling in the questionnaire: date ..... month ..... year .....

If you wish to add an important issue about the climacteric or hormone therapy, you can do it here. Thank you for filling in the questionnaire!

APPENDIX 3

HORM.TRIAL1/1999

Dear madam!

The gynaecology clinics of Tallinn and Tartu, the Institute of Experimental and Clinical Medicine and the Finnish National Research and Development Centre for Welfare and Health (STAKES) are jointly investigating the health problems of Estonian women in postmenopause and older age, specifically the **long-term health effects of postmenopausal hormone replacement therapy.** Investigations performed in other countries have revealed that hormonal replacement therapy slows down the development of osteoporosis and supposedly decreases the risk of certain cardiovascular diseases. At the same time it is thought that hormonal replacement therapy may increase the risk of breast cancer, though definitive proof of this has not been found (you will find a more detailed overview on the reverse page).

Thousands of women aged between 50-64 and selected randomly from the population register are invited to take part in this study. In order to obtain reliable results, the participants will be randomly allocated to receive either hormonal medication, substitution medicine (placebo) or no treatment at all (control group). All the women wishing to participate in this study, and having no contraindications to hormone replacement therapy, will have an equal chance to be allocated to any of these three treatment groups.

In the event that you **give your consent to participate, and you are found to be suitable to take part in the study, it will be necessary for you to visit your gynaecologist**, and where necessary you can also get advice via telephone. The clinical study will last for five years. If you wish, you can withdraw from using the study medication or start with hormone replacement therapy even if you belong to the control group. The study medication is free of charge for women in the treatment group. In the course of the trial we ask all the participants once a year to fill in a short questionnaire. Last health check will take place ten years after the beginning of the study. The results of the study will definitely help in solving the health problems of older women and increase their quality of life.

Data derived from the questionnaire and obtained at medical examination will be supplemented later and will be used for solving women's health problems and for scientific work. Your name and personal data will not be made public to anyone. Personal data will be separated from the analysable data, the latter of which is only available to a few persons involved in the study.

We would greatly appreciate if you could answer all the questions in the questionnaire and send it back to us in the attached pre-paid envelope. **We also hope that you will give your consent to take part in the study investigating the health effects of hormone replacement therapy after the end of menstruation (the time elapsed from last menstruation should be at least 12 months).** If, after completing the questionnaire—you are considered suitable for taking part in the study, we will shortly send you an invitation to the gynaecologist's reception.

If you have additional questions related to the questionnaire or participation in the study then you are welcome to call (22) 514-334 (dr. Mare Tekkel) between 9.00-12.00 on working days.

We thank you in advance for your kind cooperation!

Lee Tammemäe	Maike Parve	Helle Karro	Toomas Veidebaum	Sirpa-Liisa Hovi
Tallinn Central Hospital	Tallinn Pelgulinna	Tartu University	ECMI	STAKES,
Gynaecology Clinic	Hospital	Gynaecology Clinic	director,	Finland
Head	Head doctor	Head	professor	research scientist

The aim of the study is to investigate long-term health effects of hormone replacement therapy. We are trying to discover whether women receiving hormone replacement therapy have more or less particular diseases than women who do not receive this type of treatment. There is quite limited data available on whether combined hormone replacement therapy (estrogens together with progestins) influences the incidence of cardiovascular diseases and tumours. In order to prolong women's lifetime and improve their quality of life, it is very important to obtain reliable data about the incidence or prevention of these diseases in connection with hormone replacement therapy,

During the so-called transitional age, production of female sex hormones in ovaries decreases. In order to maintain the prior hormone levels it is possible to use **hormone replacement therapy (usually a combination of estrogens and progestins).** This type of treatment **is indicated for the alleviation of disturbances associated with transitional age and for the prevention of certain diseases.**

Estrogens are female sex hormones produced in the ovaries. In connection with the start of estrogen production, menstruations begin in teenage girls and they develop the characteristics typical of the female sex. The cessation of menstruations in middle age is also a sign of decreased estrogen production.

Estrogens play an important role in building up our bones. Due to decreases in estrogen production, loss of bone mineral density accelerates a few years after cessation of menstruations. **Hormone replacement therapy retards the loss of bone mineral density and also helps to prevent osteoporotic fractures and changes in the vertebral column.**

Estrogens are thought to have certain effects on blood coagulation and plasma lipid concentration – **they supposedly protect women from cardiovascular diseases.** This has become evident from studies with women who have voluntarily started hormone replacement therapy. Nevertheless, it is not clear whether the risk of cardiovascular diseases of these women would have been the same without hormone replacement therapy. The random allocation of women to receive either hormonal medicine, substitution medicine (placebo) or no treatment at all (control group), and long-time follow-up of these groups will ensure that the conclusions drawn from the results of the study will be reliable.

Women aged between 50–64 have a higher risk for breast cancer than younger women. Long-term replacement treatment with estrogens may increase this risk in some women. **In order to detect possible alterations at an early stage, the breasts of trial participants will be examined during each medical examination and they are also taught how to examine their breasts themselves.**

Besides estrogens the hormonal medicine also contains progestins (hormones of the corpus luteum), which have a protective action towards the endometrium. At the initial stage of treatment, progestins can cause menstruation-like bleeding, but this is not dangerous, it doesn't require special treatment and usually disappears within a few months. The intensity of the bleeding can be reduced by increasing the dose of progestin.

Based on available data it can be concluded that the possible effects of hormone replacement therapy outweigh its negative effects. Possible health problems of the women participating in the trial will be discovered early during medical examinations and are therefore easier to treat.

Original publications

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Women's views of the climacteric at the time of low menopausal hormone use, Estonia 1998

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Abstract

Objectives: This study examined women's opinions about the climacteric and hormone therapy (HT) after menopause and compared women's and physicians' opinions in a country of low-HT use.
Methods: In 1998, a postal questionnaire was sent to a random sample of 2000 Estonian 45–64-year-old women; 69% ($n = 1312$) responded. In 1999, a postal questionnaire was sent to a random sample of 500 Estonian gynaecologists and general practitioners; 68% ($n = 342$) responded.
Results: Mean age at menopause was 49.8 years (S.D. 4.0), and there was no difference by socioeconomic classes or by age in self-rated health. Ten percent of women reported having used HT, with 3% currently using it. Most women reported some symptoms, with vasomotor symptoms more frequently reported by 50–54 years old; women most often reported tiredness (48%). Half of the women but under a fifth of physicians considered the climacteric a normal phase of life. Women's awareness about HT was low and about half had no opinion on its health effects. Half of the women had visited a gynaecologist, older women less so. Women with contacts with health care were more aware of HT.
Conclusions: Women reported symptoms by age-group as similarly found in high-HT use countries and it verifies that many symptoms experienced were not due to menopause. As in other low-HT use countries, women were unfamiliar with HT and their attitudes were traditional, although physicians' attitudes were more positive. Estonian women seemed to have escaped the period of the preventive use of HT.

1. Introduction

In the clinical literature on the climacteric,[1] it has often been stated that it is a difficult period with many

[1] In this article, the climacteric is defined as the transition from premenopause to postmenopause, a conception that lay people use in Estonia and Finland. Menopause is the time of last menstruation.

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symptoms [1,2], and many practicing physicians think similarly [3]. However, epidemiological surveys on representative samples of women have shown that most problems experienced by women are due to age rather than to the climacteric [4,5]. Hormone therapy users, compared to non-users, have reported a wider range of these symptoms [6,7]. These findings suggest that medical views about the health of middle-aged women during the climacteric are likely to be based on the experiences of those seeking a physician's consultation. Views of the climacteric as a time of considerable distress and ill-health are being perpetuated and over-generalized [4,6,8]. Women's definition and understanding of menopause differs markedly from that of the health providers, health care industry or policy legislator [9].

Menopausal and postmenopausal hormone therapy (HT) is used to treat climacteric symptoms, but by 2000 long-term use for preventive purposes had became common. Recent results of experimental preventive trials on HT suggest that the benefits of HT use have been overestimated [10,11]. Physicians have been reported as prescribing HT more often than women requested [12] and the physicians' recommendations especially has an impact on women's decisions to start HT [13–15]. Based on HT sales, European countries can roughly be divided into low (2–4%)-HT use countries (Spain, Italy, Portugal, Greece and Ireland) and high (20–56%) HT use countries (Finland, Sweden, Austria, Denmark, France, Germany and the U.K.) [16]. In addition, North America is also a high-use area [17].

Most studies on women's experiences of the climacteric are based on populations where HT use is common [5]. Our study focuses on Estonia, where HT sales are low, only 10 DDD/1000 inhabitants in the study year 1998, and the value of the prescriptions was 0.39 USD/inhabitant/year. In the neighbouring country of Finland the HT sales were 48 DDD/1000 inhabitants in the same period [18], and 3.14 USD/inhabitant/year. According to the Nordic Medico Statistical Committee, in 1999 HT sales in other Nordic countries were 56 DDD/1000 inhabitants in Sweden (3.76 USD/inhabitant/year), in Norway 46 DDD/1000 inhabitants (3.42 USD/inhabitant/year) and in Denmark 29 DDD/1000 inhabitants (2.13 USD/inhabitant/year). [19]

The purpose of this study was to examine women's opinions about the climacteric and HT after menopause and to compare women's opinions to physicians' opinions in a low-HT use country.

2. Material and methods

2.1. Women's survey

An anonymous postal questionnaire was sent in 1998 to a random sample of 2000 Estonian-speaking women aged 45–64 years drawn from the Population Registry together with an invitation to join a randomised controlled Estonian Postmenopausal Hormone Therapy-trial (EPHT) on HT and with a short description of the trial. After two reminders the response rate was 69% ($n = 1312$). The questionnaire included questions about the women's experiences and views of the climacteric. Most questions had previously been used in a Finnish survey [4]. For the current survey, we used both congruent and modified questions and the questionnaire was translated from Finnish to Estonian by Estonian researchers and back to Finnish by an Estonian translator with good Finnish skills. The Estonian questionnaire was first tested by some research colleagues at TAI and then in a pilot of eight Estonian lay women between 45 and 64 years of age to make sure that the content was understandable and relevant. The women were asked, among other things, about their background characteristics, health status, menstruation, weight and height, health habits, health services utilisation, conceptions of the climacteric, and related symptoms and their management (Appendix A). The questionnaire was divided into two parts: the first was meant for all, the second only for women whose menstrual periods had ceased or who used or had used HT. Most questions had been used in an earlier Finnish population-based survey in 1989 [4]. For the purpose of the analyses, women were classified into four age-groups: 45–49, 50–54, 55–59 and 60–64 years. When comparing age-groups, 50–54 years were used as the reference group.

2.2. Estonian physician's survey

Combining physician lists from the Ministry of Social Affairs, the Estonian Gynaecologists Society and the Family Practice Society from 1999, we obtained a list of 726 gynaecologists and family practitioners

(hereafter called General Practitioner, GP). A random sample of 500 physicians (212 gynaecologists and 288 GPs) was taken. After two reminders, 342 (68%) had responded. Following the exclusion of 21 questionnaires that had not been filled in, 321 (155 gynaecologists and 166 GPs) remained. Physicians were asked who should be prescribed menopausal and postmenopausal hormone treatment and for how long [18].

The statistical significance between the groups was determined using χ^2-tests and the two-tailed *t*-test of the proportions. Odds ratios adjusting by marital status, obesity, physical exercise, smoking and alcohol consumption were calculated using logistic regression analysis.

3. Results

The mean age of the respondents was 53.9 years (S.D. 5.5), mean age at the cessation of menstrual periods was 49.8 years (S.D. 4.0), and there were no differences in the socioeconomic classes between the age-groups. Women lived mainly in urban or suburban areas, and most of them had a long education (Table 1). Women in the older age-groups were less often employed outside the home and they were more often living alone than other women.

Only 3% of the women reported current HT use (Table 1), and 10% reported having used HT at some time. In the age-group 50–54 (24% of women) HT use was somewhat more common. Compared to the 50–54-year-old women, fewer of the younger women were obese (body mass index (BMI) $\geq 30\,kg/m^2$); more than a quarter of women reported doing a lot of exercise during free time, whilst in the older age-groups women smoked less and drank less alcohol (Table 1). Less than a tenth of women daily used calcium products.

A quarter of the women rated their health as very good or good, younger women more often than older women (Table 1). Only 6% of the women reported no

Table 1
Background information of the study women and self-rated health (% of women)[a]

Age-groups (*n*)	45–49 (350)	50–54 (315)	55–59 (379)	60–64 (268)	All (1312)
Living area, urban/suburban (%)	91	91	92	90	90
Education[c]					
Basic (compulsory) <8 years	37	42	36	39	38
Secondary 9–12 years	30	29	33	34	31
University >12 years	33	30	33	27	30
Employed outside home (%)	87	84	69***	40***	72
Married or cohabiting (%)	68	66	59	48***	61
Current use of HT (%)	3	4	2	2	3
Stopped using HT (%)	4**	9	7	7	8
Obese (BMI $\geq 30\,kg/m^2$)	19**	27	27	29	25
Exercise during free time a lot[b]	24	26	30	30	27
Smoking daily	22	19	12*	9**	16***
No alcohol use	14	10	21***	27***	18***
Daily use of calcium products in previous 2 weeks	10	7	9	5	8
Self-rated health[c]					$p < 0.001$
Very good or good	32	27	21	15	24
Average	60	65	69	71	66
Poor or very poor	8	6	10	13	9
No information	0	2	0	1	1

[a] Reference 50–54 age-group.
[b] Includes "rather a lot" and "a lot".
[c] Chi-square test (tested without missing information).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 2
Symptoms in past 2 weeks by age-groups (%), proportion (%) of women reporting symptoms, and odds ratios (95% confidence intervals, CI), adjusting for marital status, obesity, physical exercise, smoking and alcohol consumption[a,b,c]

Age-groups (*n*)	45–49 (350)		50–54 (315)	55–59 (379)		60–64 (268)	
	%	OR (95% CI)	%	%	OR (95% CI)	%	OR (95% CI)
Tiredness	51	1.03 (0.76–1.40)	50	46	0.87 (0.65–1.18)	46	0.84 (0.61–1.17)
Joint/muscle ache	30	**0.64 (0.47–0.89)**	40	39	0.95 (0.70–1.29)	47	1.29 (0.93–1.80)
Headache	43	1.14 (0.84–1.55)	40	32	**0.71 (0.52–0.97)**	29	**0.62 (0.44–0.87)**
Backache	32	1.06 (0.76–1.47)	31	27	0.85 (0.61–1.18)	31	1.01 (0.71–1.43)
Sweating	24	**0.65 (0.46–0.91)**	33	29	0.83 (0.60–1.15)	25	0.70 (0.49–1.01)
Hot flashes	16	**0.41 (0.28–0.59)**	32	25	**0.69 (0.49–0.96)**	16	**0.40 (0.27–0.60)**
Irritability	22	0.82 (0.57–1.17)	26	23	0.87 (0.62–1.24)	20	0.71 (0.48–1.06)
Sleeplessness	18	0.77 (0.53–1.12)	23	23	1.06 (0.74–1.51)	22	0.99 (0.67–1.47)
Depression	20	0.80 (0.55–1.16)	24	21	0.86 (0.60–1.23)	21	0.86 (0.59–1.28)
Diarrhoea or constipation	17	0.70 (0.47–1.02)	23	18	0.77 (0.53–1.11)	22	0.99 (0.67–1.47)
Vertigo	21	1.08 (0.74–1.58)	19	18	0.89 (0.61–1.31)	21	1.13 (0.75–1.69)
No symptoms	7	1.71 (0.86–3.42)	4	8	1.93 (0.98–3.77)	7	1.77 (0.86–3.66)

[a] The 11 most common symptoms out of 17 listed and no symptoms.
[b] Reference 50–54 age-group.
[c] Statistically significant differences are shown in bold.

symptoms, and almost half reported tiredness. Vasomotor symptoms (hot flashes and sweating) were most frequently reported at the age-group 50–54, and declined after that (Table 2). For other symptoms, there was no statistically significant peak among 50–54 years old. The proportions of women reporting headaches declined steadily by age, whereas the proportion of women reporting joint or muscle ache increased. Adjusting by marital status, obesity, physical exercise, smoking and alcohol consumption did not make any difference.

The women were asked for their opinions about the climacteric through a list of statements. About 70% of the women gave their responses on the statements concerning the climacteric, about 13% could not choose and about 18% did not answer. About half of the women were of the opinion that the climacteric is a normal phase in a woman's life and does not need treatment by a physician, and that a woman does not lose her femininity during the climacteric (Table 3). The youngest women held this opinion somewhat less often. Women who had reported hot flashes and sweating or who had wanted HT or used it, more often disagreed with the statement that a woman does not lose her femininity during the climacteric. Examining women's opinions by education showed that educated women were more certain in their opinions about the climacteric and HT preventing osteoporosis (i.e. less often chose options "cannot say" or left unanswered). Furthermore, the more education a woman had, the more negative her opinion was on prescribing HT to all symptomatic women or to all postmenopausal women.

In open-ended questions women were asked to say what positive or negative features they connected with the climacteric. Positive features of the climacteric were reported by 17% of the women. Two-thirds of them said that cessation of the menstrual periods was the most positive thing because they do not have to wait for irregular bleeding, use sanitary equipment, and their intimate hygiene was easier to take care of. A quarter of the responding women were also relieved because they did not have to fear becoming pregnant any more. In addition, some women stated that they can start a new period in their lives, and they feel themselves calm, independent and matured.

Negative features in the climacteric were reported by 28% of the women. Of them, 27% mentioned the start of ageing, 20% hot flashes and sweating, 16% worsening health and diseases, 13% weight gain, and 11% irritability, mood changes and psychic instability. Some women experienced low self-esteem. Often women who reported negative features connected the climacteric with all kinds of health problems, such as tiredness and deteriorated vision.

Table 3
Women's opinion on climacteric and hormone therapy by age-group (%)[a,b]

Age-groups (*n*)	45–49 (350)	50–54 (315)	55–59 (379)	60–64 (268)	All (1312)
Climacteric is a normal phase of life					
Agree[c]	46[*]	55	57	55	53
Disagree[d]	23	19	13[*]	14	17
Femininity is not lost					
Agree[c]	49[*]	57	52	50	52
Disagree[d]	12	16	12	13	14
HT prevents osteoporosis					
Agree[c]	12	13	12	13	12
Disagree[d]	6	5	5	3	5
Cannot say	60	62	55	53	58
HT to all symptomatic women					
Agree[c]	20	20	17	14	18
Disagree[d]	22	20	18	15	19
Cannot say	39	42	42	41	41
HT to all postmenopausal women					
Agree[c]	7	7	4	6	6
Disagree[d]	25	26	27	23	25
Cannot say	48	48	43	44	46

[a] Reference 50–54 age group.
[b] In the first two questions the rest chose either cannot say or the question was not answered; in the last three the question was not answered.
[c] Includes "agree" and "nearly agree".
[d] Includes "disagree" and "nearly disagree".
[*] $p < 0.005$.

Women's opinions on HT were also studied with the use of statements (Table 3). About half of the women could not decide their opinion and a quarter gave no answer. The statement that HT prevents osteoporosis was most difficult, and only 17% of the women expressed an opinion; 12% agreed that HT prevents osteoporosis. On the statement about prescribing HT to all women showing climacteric symptoms, 37% of women gave an opinion: one half of them agreed and the other half disagreed. When stating that HT should be prescribed to all postmenopausal women, only 6% of the women agreed and a quarter disagreed. Women who had used any drugs, who had visited health care several times within the past 12 months, or who had wanted to use or had used HT agreed more often than other women with the statements that HT prevents osteoporosis, that HT should be prescribed to all women with menopausal symptoms and that HT should be prescribed to all postmenopausal women.

When the women were asked from where they had obtained information on the climacteric, the media was often mentioned 55% of women, friends or relatives were mentioned by 35% of the respondents, and 25% from a gynaecologist. When women were asked with whom they had discussed the climacteric, 39% had not discussed it with anybody, 18% had discussed it with their husband or partner, 36% with friends and 21% with relatives.

Most of the women (69%) had visited a physician within the previous 12 months, and three or more visits were reported by 30% of respondents. There were no differences between the age-groups. About 40% of the women had visited a gynaecologist in the previous 12 months, and the proportions visiting were lower in the older age-groups: half of 45–49 and 50–54 years had visited, but 29% of 60–64 years old. Likewise, the proportion of women with three or more decreased, from 10% among 45–49 years old to 2% among 60–64 years old.

When asked about visits to a physician due to climacteric symptoms, 389 women (30% of the visitors) gave specific reasons. Irregular menstruation (33% of the responders), and hot flashes and sweating (30%) were mentioned most often. Other reasons given were

Table 4
Comparison of women's and Estonian physicians' opinions on climacteric and HT (%)[a]

n	Women (1312)	Gynaecologists (155)	General practitioners (166)
Normal phase of life, needs no HT	53	6***	15***
HT for all symptomatic women	18	48***	36***
HT for all postmenopausal women[b]	6	37***	17***

[a] Reference: women.
[b] Without contraindication.
*** $p < 0.001$.

different gynaecological problems like fibroids (10%) and psychological reasons like depression, tiredness, irritability (11%). When asked what climacteric symptoms women had, 285 women (22%) responded: most common symptoms were hot flashes (55%), irregular periods (16%) and psychological reasons such as irritability, depression and sleeplessness (24%).

Some 10% of women had used HT; the most common reasons for using HT were hot flashes and sweating, irregular periods, and climacteric symptoms. Some women expected better self-esteem with HT.

Women's opinions on the climacteric and HT were very different from Estonian physicians' opinions (Table 4). More than half of the women agreed with the statement that the climacteric is a normal phase of life and it needs no HT, but less than a sixth of physicians were of the opinion that HT use was not necessary during the climacteric. On the statement about prescribing HT for all symptomatic women, less than a fifth of the women agreed, but almost a half of the gynaecologists and over a third of the GPs agreed with the need to prescribe HT for all symptomatic women. Every fifth GP and every fourth gynaecologist but only every sixteenth woman favoured prescribing HT for all postmenopausal women.

4. Discussion

As anticipated from sales figures, HT use in Estonia was low, 3% reported current use of HT and only 10% in total had ever used HT. Accordingly, women were not familiar with HT and most of them could not take a stand on its health benefits. This was in contrast with the favourable opinions of Estonian physicians. Women who had contacts with health care (e.g., used drugs, several visits to physician) shared physicians' opinions about HT more often than other women.

The response rate of 69% in our study is fairly good. It is possible that the invitation to join a trial reduced women's willingness to return the questionnaire.

In Estonia, many women had the opinion that the climacteric is a normal phase in a woman's life which does not need medical treatment, and femininity is not lost in the climacteric. This contrasts with physicians' opinions where only a small proportion stated that the climacteric do not need medical treatment, gynaecologists less often than GPs [18]. However, compared to the Finnish survey in 1989 [4], Estonian women had a more negative opinion on the climacteric. In Estonia half of the women agreed that femininity is not lost at the climacteric, but in Finland 78% of the women had this opinion. In Estonia the youngest age-group had the most negative opinion, whereas in Finland the youngest age-group had the most positive opinion of the climacteric with regards to femininity. Similar differences between the countries were found in regards to the statement of the climacteric as a normal phase of life.

Estonian women who had more contacts with health care and who had used HT had more negative opinions about the climacteric and more positive opinions about HT than other women. This suggests professional influence in the diffusion of HT. Awareness about the climacteric and hormone treatment seems to correlate to use of HT [20–22], and that physicians' recommendations to use HT influence women [12–15]. However, education increased negative opinions about HT.

When compared to Finnish women, fewer Estonian women reported positive experiences of the climacteric in an open-ended question (17% versus 30%). However, the most common issues (relief at the end of menstrual periods and an end to the fear of pregnancy) were similar. Similar findings were also found in a Danish study [23]. In both Finland and Estonia just as many women reported negative aspects

of the climacteric, but the reasons varied. In Estonia, almost a third of responding women said that it is the beginning of ageing, but in Finland only 2% said this.

Even though the Finnish survey is 10 years older than the Estonian study, HT use was common and menopause and the climacteric had been widely discussed [24]. It is possible that the public discussion had influenced women to have a more positive opinion of the climacteric, regardless of drug treatment. Anyway, Søgaard and colleagues found that women with high education and the most awareness of estrogen were more unwilling to use estrogen to prevent chronic diseases because they criticised the fact that too little is known about HT [21,25].

Estonian women in the age-groups 50–54 and 55–59 years rated their health better than Finnish women [4], even though they reported more symptoms. The proportions of women reporting vasomotor symptoms were similar in the two countries and in both countries more 50–54-year-old women reported vasomotor symptoms than other women. These results support the claim that vasomotor symptoms depend on menopausal status and the other symptoms are related to age. The etiology of hot flashes is not known [26], but women using HT have been reported as receiving help for vasomotor symptoms, but not for the other symptoms [7,27].

The concept of menopausal symptoms needs to be clarified. Middle-aged women report a lot of other symptoms, but they are not specific to menopause. The different symptom lists describe the usual subjective health problems, many that become more common with age rather than due to menopause. Furthermore, a survey on middle-aged men showed that men report similar symptoms [28]. Classifying all symptoms of middle-aged women as either menopausal or climacteric creates a misleading picture of the aging of women.

Estonian women seemed to have escaped the period of preventive use of HT. Their attitudes to the climacteric in 1998 were still traditional and knowledge and use of HT was low, although physicians were already enthusiastic [18]. In the 1990s professional journals contained only a few articles about HT [29]. Many women responded that the media was a source for learning about the menopause. However, we have no systematic data on what and how menopause and HT were discussed in the media. Experimental and other research [11,30–31] have now shown that combined oral estrogen/progestin does not prevent cardiovascular diseases; long-term use may increase the risk of breast cancer; it does not prevent dementia [32–33], protect cognition [34] or increase quality of life [35]. On the contrary, HT may increase coronary heart diseases during the first year of treatment [36], and increase the risk of ischemic stroke [37]. The results from the Women's Health Initiative (WHI) estrogen-alone trial also show negative results on prevention of cardiovascular diseases [38], dementia [33], and cognition [34]. Thus, HT use in Estonia may remain low, and be restricted to symptomatic use.

Appendix A

Questions used from the women's questionnaire

Do you live
1. in a town centre
2. outside of the town centre/in a suburban area
3. in a village
4. in the countryside outside of a village

What is your general education

What is or was your occupation/profession? _____

Are you currently
1. in a paid job
2. working at home
3. a pensioner
4. unemployed
5. something else, specify _____

What is your current marital status
1. single
2. married
3. cohabitant
4. divorced or separated
5. a widow

Your height is _____ cm

Your weight is _____ kg

What is your current health?
1. good
2. rather good
3. moderate
4. rather poor
5. poor

During the past two weeks, have you had any of the following symptoms or problems?
1. dizziness
2. tiredness
3. diarrhea or constipation
4. irritability
5. constant cough
6. depression
7. backache
8. stomach pain
9. headache
10. joint/muscle ache
11. shortness of breath
12. hot flashes

13. sore throat
14. sleeplessness
15. loss of appetite
16. menstrual problems
17. sweating
18. no symptoms

Have you ever discussed the climacteric with any of the following persons? Choose several, if appropriate.
1. friends
2. relatives
3. husband/companion
4. someone else, who? _____
5. with no one

Have you received information about the climacteric from any of the following sources? Circle after every statement the number which corresponds best your opinion

	a lot	somewhat	not at all
1. gynaecology	1	2	3
2. other physician	1	2	3
3. midwife, nurse or doctor's assistant	1	2	3
4. friends or relatives	1	2	3
5. newspapers, books, radio, television	1	2	3
6. other source, specify	1	2	3

During the last 12 months have you visited a physician (excluding dentist)
1. no
2. 1-2 times
3. 3-4 times
4. 5-6 times
5. 7 times or more

During the last 12 months have you visited a gynaecologist
1. no
2. 1-2 times
3. 3-4 times
4. 5-6 times
5. 7 times or more

Have you wanted hormone therapy because of climacteric
1. no
2. yes, why? _____
3. I don’t remember

In the following we give some statements about climacteric and hormones (estrogens or estrogens combined with progestins) used during climacteric and postmenopause. In each case circle the alternative which best describes your opinion.

	I totally agree	I somewhat agree	I don't know	I somewhat disagree	I totally disagree
Hormones effectively prevent osteoporosis	1	2	3	4	5
Climacteric is a normal phase in a woman's life and usually doesn't need a doctor's treatment	1	2	3	4	5
Hormones should be given to all middle-aged women having (menopausal) symptoms	1	2	3	4	5
A woman does not lose her femininity during climacteric	1	2	3	4	5
Hormones should be given to most postmenopausal women	1	2	3	4	5

What are the positive sides of climacteric?
1. I find nothing positive in it
2. positive is _____
3. I cannot say

What are the negative sides of climacteric?
1. I find nothing positive in it
2. positive is _____
3. I cannot say

When did you have your last menstrual periods
1. over 12 months ago
2. 3-12 months ago
3. less than 3 months ago
4. other, specify _____

How much do you exercise during your free-time?
1. not at all
2. a little
3. somewhat
4. quite a lot
5. a lot

During the past two weeks have you used calcium products
1. daily
2. every now and then
3. not at all

Do you currently smoke?
1. no

2. yes. occasionally
3. yes, _____ cigarettes daily

How much alcohol do you use?
1. a lot
2. quite a lot
3. a reasonable amount
4. rather little or little
5. not at all

Have you used female hormone therapy?
1. no
2. yes, when did you start? year_____month_____
3. I am not yet in the climacteric

Have you visited a physician because of climacteric symptoms? Choose several, if appropriate.
1. yes, I have visited a gynaecologist.
2. yes, I have visited another physician.
3. no, I have not visited a physician, but I have considered it.
4. no, I have not even considered visiting a physician.
5. I have no climacteric problems.

What were the climacteric problems which made you to visit a physician?
1. I have not visited a physician because of the climacteric.
2. I visited. Why?_____

Have you had climacteric symptoms?
1. no
2. yes. What_____

Why was your hormone therapy prescribed (give all the reasons)
1. I got hormone treatment in climacteric. Why _____
2. I got hormone treatment in postmenopause. Why? _____

Have you stopped the hormone treatment?
1. I have never taken hormone therapy
2. I am still taking hormone treatment
3. I stopped taking hormone treatment. When? _____

Why did you stop hormone treatment?
1. the treatment was planned only for a certain period
2. I wanted to stop by myself. Why _____
3. the physician told me to stop. Why _____
4. other reason. What _____

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Comparison of Estonian and Finnish physicians' opinions of menopause and hormone therapy

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Abstract

Objective: To compare Estonian and Finnish gynaecologists' and general practitioners' (GP) opinions on and prescribing practices in hormone treatment (HT) during and after menopause.

Methods: Data was collected using similar postal questionnaires. In 2000 in Estonia, a random sample included 212 gynaecologists and 288 GPs (68% responded); and in 1989 in Finland, 100 male and 100 female gynaecologists, 100 general practitioner specialists and 100 non-specialists (73% responded). Gynaecologists and GPs were compared to each other within the countries, and the two countries were compared within the specialities.

Results: Gynaecologists' opinions of benefits were positive and similar in Estonia and Finland, and more positive than those of GPs. Gynaecologists and GPs in both countries had similar opinions about harms. Gynaecologists were in favour of longer HT than GPs, and longer treatment was recommended in Finland than in Estonia. In both countries a large proportion of physicians (48% of gynaecologists in Estonia and 65% in Finland) stated that they would routinely prescribe HT to all women at menopause without contraindication, regardless of symptoms, and some (31% of gynaecologists in Estonia and 19% in Finland) favoured routine prescribing to all postmenopausal women.

Conclusions: Estonian physicians' positive attitudes suggest increased use of HT. Comparisons of the two countries and specialities suggest that physicians' positive opinions may long predate increased use.

Keywords: General practitioners; Gynaecologists; Hormone treatment; Menopause

1. Introduction

The use of oestrogen and progestin drugs during and after menopause (hereinafter hormone treatment (HT)) is widespread but varies considerably from one Western country to another. At the beginning of the 1990s, HT usage was greatest in the United States and the United Kingdom; Scandinavian countries, including Finland, were in the middle group [1]. The variation cannot be explained by morbidity, and it has been suggested that one reason is the varying attitudes towards HT of physicians in different countries.

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Finland is a Western country with a market economy and is a member of the European Union. In Finland, HT became common in the 1980s [2,3], and its use is still increasing. In the past 12 years, the use of HT has almost doubled among 55–59-year-old women (from 25% in 1989–46% in 2001), and it has increased three-fold (from 14 to 46%) among 60–64-year-olds. [4,5] (unpublished data from NPHI in 2002). Topo et al. [6] found that physicians offered HT more often than women asked for it.

Estonia regained its independence in 1991, after being a constituent republic of the socialist Soviet Union for five decades. Estonia is a transition state which has been changing rapidly into a capitalist, market-oriented country and is joining the European Union in 2004. In this environment, medical care is likely to follow trends in the market-oriented countries. [7] This offers an opportunity to study physicians' opinions on HT in a rapidly changing situation.

In the 1990s, the use rate of HT in Estonia was very low (Fig. 1). Sales increased until 2000. In 1998, it was at the same level as that of 1982 in the neighbouring country of Finland, where HT use has steadily increased since 1982.

The purpose of this study is to describe Estonian gynaecologists' and general practitioners' (GP) opinions on the benefits and harms of HT, and their prescribing practices, and to compare them to those of Finnish gynaecologists and GPs. In 1989, a survey in Finland showed physicians had favourable attitudes towards HT [8]. In 1998, the Finnish guidelines on HT were still positive and recommended wide indications. A comparison of Estonian and Finnish physicians' opinions and practice is interesting, because the use rate of HT is still low in Estonia. Comparison provides data that allows speculation on the relation between use and physicians' opinions over time.

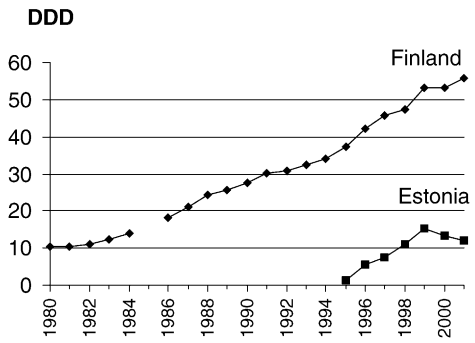

Fig. 1. Sales of (post)menopausal hormones in Estonia and Finland in defined daily doses (DDD) per 1000 of population per day during the period 1981–2001; ATC-classes G03C, E and F.

2. Material and methods

Data was collected using postal questionnaires in 2000 in Estonia and in 1989 in Finland. The questionnaires were anonymous, and the respondents were asked to send their name tags in a separate envelope to avoid receiving a reminder.

2.1. Estonian physician survey

Combining physician lists of the Estonian Health Ministry, Gynaecological Society and Family Practice Society, we obtained a list of 726 gynaecologists and family practitioners (later called general practitioner). After the exclusion of 30 physicians without proper addresses, the names were organised in alphabetical order and numbered. The random number procedure in Excel was used to create a random sample of 500 physicians (212 gynaecologists and 288 GPs). All physicians received a questionnaire in Estonian mentioning the availability of a Russian version on request; five physicians asked for this. After two reminders, 342 (68%) had responded. Following the exclusion of 21 questionnaires that had not been filled in (physicians defining themselves as not part of the target population), 321 (155 gynaecologists and 166 GPs) remained. The distribution of respondents by speciality and sex corresponded well to the sample; we do not know the distribution of other background characteristics in the sample.

2.2. Finnish physician survey

A random sample of 500 Finnish physicians, stratified by speciality (and for gynaecologists, by gender), was identified from the physician register at the National Board of Health. After two reminders, 357 (74%) responded. The sample included 100 male and 100 female gynaecologists, 100 internists, 100 general practitioner specialists and 100 non-specialists.

Of the responding 58 non-specialists, 33 were truly non-specialists, and they were included in the category of GP. In this study, only gynaecologists and GPs are included (response rate 73% (293)). The number of gynaecologists was 151 and that of GPs was 101. Although the sample for gynaecologists was classified by gender, there were no differences between women and men [8], and they were combined in this study.

Questionnaires included questions on current patient load, prescribing frequency of HT, benefits and harms of HT, and to whom HT should be prescribed and for how long. In the questionnaire, HT was first defined as hormone therapy used during "climacteric" and afterwards referred to by the local lay expression. The questionnaire included explanations of "climacteric" and "postclimacteric". The literal translation of postmenopausal hormone therapy was "postclimacteric hormone therapy" in Finnish and " preventive hormone replacement therapy" in Estonian.

The questions used in this study were similar in the two surveys. The Finnish questions had been tested and used [8]. The Finnish questions were translated into Estonian by a native Estonian translator, the content was reviewed by two Estonian gynaecologists, and filling in of the questionnaires was tested by four Estonian physicians.

Gynaecologists and GPs were compared to each other within the countries, and the two countries were compared within the specialities. Adjustment for age, workplace and gender was made by logistic regression. The SAS system for Windows V8 was used. Testing the statistical significance of the differences was done by the *t*-test, χ^2-test and odds ratios (OR) with 95% confidence intervals.

3. Results

In Estonia, both gynaecologists (90%) and GPs (92%) were mainly women, whereas in Finland, the minority of GPs (35%) were women; because of the sampling method employed, half (100) of the Finnish gynaecologists were women. In both countries, gynaecologists were older than GPs: in Estonia, the mean year of university graduation was 1975 for gynaecologists and 1980 for GPs; in Finland, 1971 and 1975, respectively. Gynaecologists more often worked in the capital area than GPs.

In Estonia, both gynaecologists and GPs had more menopausal and postmenopausal patients per week than in Finland. In Estonia, there were no differences between gynaecologists and GPs as regards the number of menopausal patients per week; both reported on average 17–18 women, but GPs had more older women patients whom they defined as postmenopausal ($n = 23$) than gynaecologists did ($n = 11$). In Finland, gynaecologists met larger numbers of both menopausal ($n = 13$) and postmenopausal ($n = 9$) women than GPs did, of whom one fifth said that they did not have any menopausal or postmenopausal patients.

When physicians' opinions about benefits and harms of HT were asked, both Estonian and Finnish physicians had very favourable attitudes—gynaecologists more often than GPs (Table 1). Generally, more Estonian than Finnish physicians reported benefits. Almost all respondents were of the opinion that HT contributes to the prevention of osteoporosis. In both countries, gynaecologists more often than GPs said that HT contributes to the prevention of cardiovascular diseases and to improved subjective well-being. In Estonia, about 80% of respondents said that a delay in ageing was one result, whereas in Finland less than half said so. On the other hand, both Finnish gynaecologists and GPs more often stated that improved subjective well-being was a benefit than Estonian gynaecologists or GPs did. Adjustment for age, workplace and gender did not notably change the differences between the specialities or countries. The only major change was that after adjustment between Estonian gynaecologists and GPs in regards to choosing prevention of breast cancer as a benefit, became statistically significant (Table 1).

When physicians were asked about harms of long-term HT, Estonian GPs mentioned more harms than did gynaecologists. Both groups considered that harms included breast cancer, uterine cancer and the return of menstruation. In Finland, 90% of gynaecologists mentioned that the return of menstruation was a harm, as did 60% of GPs. Finnish GPs mentioned more often than gynaecologists that uterine cancer and cardiovascular diseases were harms.

Physicians were asked to whom they would recommend HT at menopause. In Estonia, physicians were able to choose more than one alternative, but the percentages were calculated by choosing the most

Table 1
Physicians' opinions on benefits and harms of combined postmenopausal estrogen–progestin therapy, % of physicians giving an affirmative answer, and raw and adjusted OR (95% confidence limits) between gynaecologists and GPs

	Estonian				Finnish			
	% Gyn (155)	% GP (166)	Raw OR[a] (95% CI)	Adjusted OR[b] (95% CI)	% Gyn (151)	% GP (101)	Raw (95% CI)	Adjusted OR[b] (95% CI)
Benefits								
Prevention of								
Osteoporosis	94	93	1.15 (0.46–2.86)	1.61 (0.59–4.42)	96	92	1.26 (0.37–4.24)	1.24 (0.32–4.71)
Cardiovascular disease	87	76	2.03 (1.13–3.62)	3.73 (1.85–7.54)	74	52	2.72 (1.60–4.63)	2.48 (1.38–4.43)
Breast cancer	6	11	0.48 (0.21–1.09)	0.40 (0.16–0.97)	3	6	0.66 (0.19–2.33)	0.46 (0.11–1.83)
Uterine cancer	21	15	1.47 (0.82–2.61)	1.45 (0.79–2.68)	25	13	2.28 (1.14–4.53)	2.22 (1.06–4.66)
Improved subject well-being	86	67	3.00 (1.72–5.22)	3.74 (2.02–6.91)	98	81	6.92 (2.24–21.37)	7.45 (2.17–25.51)
Delay of ageing	79	82	0.85 (0.49–1.48)	0.72 (0.39–1.31)	48	38	1.23 (0.74–2.04)	1.30 (0.74–2.25)
Decreased weight problems	15	13	1.20 (0.64–2.27)	1.10 (0.56–2.16)	6	3	2.07 (0.55–7.84)	1.45 (0.35–6.00)
Harms								
Increased risk of								
Cardiovascular disease	3	2	1.07 (0.26–4.37)	0.93 (0.20–4.19)	3	12	0.21 (0.07–0.61)	0.19 (0.06–0.61)
Breast cancer	50	51	0.97 (0.62–1.50)	1.15 (0.71–1.87)	47	37	1.35 (0.81–2.26)	1.30 (0.74–2.26)
Uterine cancer	27	33	0.73 (0.45–1.17)	0.76 (0.45–1.27)	11	21	0.45 (0.22–0.92)	0.39 (0.18–0.86)
Return of menstruation	25	32	0.72 (0.44–1.17)	0.65 (0.39–1.11)	90	61	5.47 (2.80–10.76)	4.27 (2.08–8.76)
Increased weight problems	21	30	0.62 (0.37–1.04)	0.62 (0.36–1.08)	21	18	1.19 (0.63–2.27)	1.19 (0.59–2.40)

[a] Reference group GP.
[b] Adjusted for age, sex and workplace; the reference group is GP.

Table 2
Physicians' opinions on recommending HT, by speciality, % of physicians

	Estonian		Finnish	
	Gyn (155)	GP (166)	Gyn (151)	GP (101)
PHT for menopausal problems				
For all women[a]	48*	36	65***	37
Selectively	47*	58	35***	60
No opinion or response	5	5	0*	3
Total	100	100	100	100
PHT in postmenopausal phase				
For all women[a]	37***	17	19**	7
All at risk of osteoporosis	22	25	25	16
Individually at risk of osteoporosis	38**	52	50**	66
Only exceptionally	0	1	1**	8
Other, no information	3	5	5	3
Total	100	100	100	100

[a] Without contraindication.
* $P < 0.05$.
** $P < 0.01$.
*** $P > 0.001$.

Table 3
Physicians' opinions on duration of PHT; in years by speciality, % of physicians

	Estonian		Finnish	
	Gyn (155)	GP (166)	Gyn (151)	GP (101)
No treatment	6	15	1	2
5	37	24	15	25
6–10	26	17	19	6
11–20	5	5	16	11
For the rest of life	11	13	31	26
No opinion	4	16	2	26
Other, no information	11	9	17	5
Total	100	100	100	100
χ^2-test	0.0005		<0.0001	

widespread indication. In both countries, a large proportion of physicians stated that they would routinely prescribe HT for all women at menopause with no contraindication—regardless of symptoms (Table 2). In both countries, gynaecologists would recommend such use of HT more often than GPs, but in Estonia less frequently than in Finland. There was no difference between the countries with regard to GPs' recommendations.

When asked to whom physicians would recommend HT after menopause, some physicians in both countries favoured routine prescribing to all women—more frequently in Estonia than Finland (Table 2). In both countries, routine prescribing for all women was more commonly reported by gynaecologists than by GPs. In Estonia there were no differences between the specialities in recommending HT to all women at risk of osteoporosis, but in Finland gynaecologists stated that they would recommend HT more often than was the case with GPs. Of the Finnish GPs, 8% reported that they prescribe HT for postmenopausal women only in exceptional cases, whereas among Estonian physicians hardly any stated this. Gynaecologists in Estonia favoured prescribing HT for postmenopausal women more commonly than did gynaecologists in Finland (OR, 3.37 (1.80–6.33)).

On the other hand, when physicians were asked about the length of HT, Estonian physicians favoured shorter periods of treatment than Finnish physicians (Table 3). In Estonia, one-third of GPs would not recommend HT at all or had no opinion, whereas only 10th of gynaecologists would not recommend it or had no opinion. The treatment lengths of those GPs who did prescribe HT were similar to those of gynaecologists. In Finland, many GPs did not have an opinion concerning the length of treatment. Those who gave it prescribed somewhat shorter treatment than gynaecologists. Estonian gynaecologists favoured shorter treatment periods than their Finnish colleagues; 47% of Finnish gynaecologists and 37% of Finnish GPs recommended HT for a period of more than 10 years or for the rest of the woman's life.

4. Discussion

Physicians' opinions concerning HT seemed to depend more on their speciality than their country of residence or their age and sex. Gynaecologists in both countries studied mentioned benefits of HT more often than GPs, and they were in favour of longer treatment periods than GPs. Finnish gynaecologists favoured longer treatment periods than their Estonian counterparts.

Previous research suggests that a physician's positive attitude towards HT seems to increase his or her tendency to prescribe it [9,10], and physicians tend to

recommend HT more often than women want [6]. In Norway and Sweden, but not in Denmark, older gynaecologists prescribed HT more often than younger ones [11]. The use of HT is higher among female gynaecologists and the spouses of physicians than among other women [10–12]. In the USA, female physicians were more likely to prescribe HT than male physicians [9], and medical condition did not predict the duration of HT use among medicaid recipients [13]. Direct advertising did not have as much effect on prescribing as sponsored travel or education [14].

In Estonia, gynaecologists more often than GPs considered drug advertising to be a factor contributing to increased HT use [7]. In a drug company survey ($n = 309$) carried out in 2000 (45% response rate), 65% of the female gynaecologists reported current or past use of HT. Almost all (95%) of the younger gynaecologists said that they will use HT [15].

The use of HT is low in Estonia. Estonian physicians' positive attitudes suggest that very probably the use of HT will increase. The discrepancy between Estonian physicians' opinions and the low level of use shows that opinions may predate use by many years. In Finland, a similar relationship was found between opinions in 1989 and increase in use in the 1990s.

In spite of the 11 years elapsing between the questionnaires, physicians' opinions are very similar in Estonia and Finland. At the time of the Finnish survey assumed cardioprotective effects of estrogens were based on observational studies suggesting a risk reduction among HT users [16,17]. Observational data had also supported HT benefits for bone mineral density [18,19]. Randomised controlled trials on HT were lacking at that time. Between the two questionnaires, 1989 and 2000, one large randomised controlled trial on postmenopausal hormone therapy, The Heart and Estrogen/progestin Replacement Study (HERS), was completed. Its conclusion was that HT increases the risk of venous thromboembolism in women with coronary heart disease [20]. Its results cannot be seen in the Estonian study: most Estonian physicians, and more so than in Finland, believed that HT contributes towards the prevention of cardiovascular diseases.

At the time of the survey, the official indications on HT in Estonia were climacteric complaints or urogenital disorders due to lack of estrogens, primary ovarian failure, and prevention of osteoporosis in postmenopause. The contraindications were breast cancer or any other oestrogen-dependent cancer or suspicion of it, bleeding from the genital tract with an unclear reason, acute thrombophlebitis or thromboembolism, and active liver disease. In our survey, Estonian physicians gave much wider indications, including to improve subjective well-being and to delay ageing. Most physicians stated prevention of cardiovascular diseases to be a benefit. The first guidelines for HT in Estonia were published in 2001, some months after our survey. These indications for preventive purposes included a risk of cardiovascular diseases (including problems caused by smoking) and the incidence of cardiovascular disease in a close relative [21]. (In the December 2002 version, cardiovascular diseases do not appear any more.)

In both countries, gynaecologists had a more positive opinion of HT than GPs did. More physicians chose the option of not prescribing HT when asked the length of therapy than when asked to whom they prescribe. This suggests that the latter question might have tempted physicians to mention more indications than what they might choose in real life. However, this should not influence the comparison between the two specialities.

After Estonia gained independence from the Soviet Union at the beginning of the 1990s, the prescribing of HT was in practice left to gynaecologists. In Finland, however, this is not the case, and this situation is an unlikely explanation for positive opinions. Rather, professional interests and promotion activities may have been important. Gynaecologists have been the main target for postgraduate education on HT conducted by the drug industry [7].

According to current trials [22], it can be assumed that the prevention of osteoporosis will be promoted as an important indication for long-term HT. And because Estonian gynaecologists and GPs unanimously agree with regard to this benefit, the indication is likely to remain. In addition to preventing fractures, it decreases the rate of colorectal cancer. [22–24]. On the other hand, results from recent randomised clinical trials show that HT, at least combined oestrogen–progestin regimens, increase the occurrence of various other diseases, including breast cancer and cardiovascular events [22–24]. Among older women, HT did not improve the health-related quality of life or other psychosocial outcomes [25].

HT increased the risk of dementia and did not prevent mild cognitive impairment [26], and HT increased the risk of clinically meaningful cognitive decline [27]. It remains to be seen if these recent results from randomised clinical trials will change the Estonian and Finnish physicians' opinions on HT and, as a consequence, their prescribing practices.

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Who wants to join preventive trials? – Experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]

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Abstract

Background: The interest of patients in participating in randomized clinical trials involving treatments has been widely studied, but there has been much less research on interest in preventive trials. The objective of this study was to find out how many women would be interested in a trial involving postmenopausal hormone therapy (PHT) and how the women's background characteristics and opinions correlated to their interest.

Methods: The data come from recruitment questionnaires (n = 2000) sent to women in Estonia in 1998. A random sample of women aged 45 to 64 was drawn from the Population Registry. The trial is a two-group randomized trial comparing estrogen-progestogen therapy with placebo or no drugs. A brief description of the study was attached to the questionnaires. Women were not told at this stage of the recruitment which group they would be assigned to, however, they were told of the chance to receive either hormone, placebo or no treatment.

Results: After two reminders, 1312 women (66%) responded. Eleven percent of the women approached (17% of the respondents) were interested in joining the trial, and 8% wanted more information before deciding. When the 225 women who stated clearly that they were interested in joining and the 553 women who said they were not interested were compared, it was found that interested women were younger and, adjusting for age, that more had given birth; in other respects, the sociodemographic characteristics and health habits of the interested women were similar to those of the non-interested women. The interested women had made more use of more health services, calcium preparations and PHT, they were more often overweight, and more had chronic diseases and reported symptoms. Interested women's opinions on the menopause were more negative, and they favoured PHT more than the non-interested women.

Conclusion: Unlike the situation described in previous reports on preventive trials, in this case Estonian women interested in participating in a PHT trial were not healthier than other women. This suggests that trials involving PHT are more similar to treatment trials than to preventive trials. In a randomized controlled trial, more information should be obtained from those women who decline to participate.

Background

Randomized controlled trials (RCTs) are needed so as to avoid bias in scientific research. There are many studies and reviews on factors that promote or hinder interest in participating in treatment trials – both in regard to patients and physicians [see e.g. [1-4]]. Men, patients who are older, less educated and from lower socioeconomic backgrounds, non-whites, smokers, and persons lacking adequate social support are more willing to participate in clinical trials. Furthermore, they tend to be more severely ill than those who do not participate. Identified obstacles include patients' and physicians' disapproval of patients' serving as research subjects, a lack of altruistic motives, distrust of the medical profession, a lack of knowledge of what is required of trial participants, and preference for a certain treatment. Many patients do not understand the reasons why treatments should be allocated at random, and this is an important reason why patients choose not to join randomized clinical trials. [5-8]. Disinterest on the part of patients and physicians in participating in clinical trials constitutes a threat to the generalizability of RCTs [9].

There has been much less research on participation in trials studying preventive measures (preventive trials). The data available thus far suggest that there is a difference in the types of people who join preventive trials and treatment trials. Participants in preventive trials tend to be better off than non-participants as regards socioeconomic situation, health habits and health [10-14]. However, most evaluative studies have failed to document adequately the characteristics of persons who were eligible but did not participate [1]. Less is known of physicians' motivation as regards including or encouraging people to participate in preventive trials [15]. Preventive drug therapy, and thus trials involving such drugs, are likely to increase in the future, and more information is needed on who wants to take part in preventive trials. Such data are useful in order to increase the recruitment rate as well as to interpret trial results.

By means of a mailed questionnaire in the Estonian Postmenopausal Hormone Therapy (EPHT)-trial, we recruited healthy 45–64-year-old Estonian women for studying the long-term (5-year) health effects of PHT. The trial investigated the immediate effects of PHT on well-being and symptoms, impacts on the experience of the climacteric, on aging and partner relationships, and influences on the use of health services. Furthermore, the trial investigated the placebo effect and trial effect by means of the design as well as their effect on recruitment and compliance. The object of this paper is to report on how many women were interested in participating in such a trial and how sociodemographic characteristics, health, health habits, health services utilization and opinions regarding the menopause and aging influence women's interest.

Methods

The trial is a two-group randomized trial comparing oestrogen-progestogen therapy to placebo or no drugs carried out in Estonia. The participants were allocated to four random arms forming two groups: the blind group was given an active drug or a placebo, and the non-blind group was given an active drug or no treatment. Women were informed that drugs would be provided for five years. A random sample of women aged 45 to 64 was drawn from the Population Registry and questionnaires were sent to the women. A brief description of the study was attached to the questionnaire and women were invited to participate in the trial if they were found to be eligible. In the letter, women were told about the sampling; that the trial investigated the health problems of perimenopausal and older women in Estonia, especially the long-term effect of hormonal replacement therapy after cessation of periods; and that the drugs would be provided for five years. In this first letter, women were not presented with the trial design in detail, but they were told that the women will be randomly divided into groups of hormone treatment, placebo, or no tablets. Further, they were told that physician examinations will be provided annually, and the possible risks and benefits of PHT were explained. The study plan had been accepted in the Committee of Medical Ethics in Tallinn. The first 2000 women, in the sample of spring 1998, were sent a more detailed questionnaire, which provided more information on the respondents. After two reminders, the response rate was 66% (n = 1 312).

The questions used in this article were structured, with fixed alternatives. As regards current health, women were asked to choose between very good, good, average, poor or very poor; "very good" and "good" were later combined to "good". To measure health status, women were asked if they had or had had chronic diseases, such as cancer (breast, uterus, ovary), myocardial infarction, cardiac failure, hypertension, stroke, thromboses, liver diseases, renal failure, diabetes or icterus. In the case of other symptoms, women were given a checklist of 18 different symptoms or health problems and asked to choose all that they had experienced within the past two weeks. In the case of health habits, questions on current smoking, alcohol consumption and exercise were asked. The choices for current smoking were: no, yes every now and then, and yes daily, how many cigarettes per day. The choices for alcohol consumption were not at all, low, moderate, fairly high and high. Exercise in leisure-time was elicited using the choices not at all, a little, some, a lot, a large amount; "a lot" and "a large amount" were later combined to "plenty of exercise". Body mass index (BMI) was calculated by

Table 1: Distribution of women by their interest in participating in a randomized PHT preventive trial in Estonia and comparisons of the background characteristics of women according to their interest in participating. [1)]

	Interested (n = 225) (% = 11)	Want more information (n = 163) (% = 8)	Do not know (n = 371) (% = 19)	Non-interested (n = 553) (% = 28)	All respondents (n = 1312) (% = 66)	No reply (n = 688) (% = 34)
Median age, years [2)]	51	53	53*	56***	54	53*
Lives in the capital, %	68	64	67	62	65	76 [3)]
Married or cohabiting, %	62	64	63	58	61	
≥ 12 years of education, %	64	62	60	61	61	
In employment, %	78	72	73	67	70	
Given birth, %	92	92	89	85[4)]	87	

[1)] Adjusted for age
[2)] Statistically significant: * $p < 0.05$, *** $p < 0.0001$ compared to the "interested" group
[3)] Age adjusted OR 0.64 (CI 0.46 0.90), reference group "interested"
[4)] Age adjusted OR 2.00 (CI 1.16 3.46), reference group "interested"

Table 2: Comparison of health service utilization of women interested and not interested in participating in a randomized PHT preventive trial in Estonia, proportion (%) of women, and age-adjusted odds-ratios (OR).[1)]

	Interested (n = 225) %	Non-interested (n = 553) %	OR (95% CI)[1)]
Physician visit in past year	76	68	1.53 (1.06–2.20)
Gynaecologist visit in past year	53	39	1.40 (1.01–1.94)
Used calcium drugs in last 2 weeks	32	23	1.49 (1.04–2.13)
Used PHT at some time [2)]	26	11	2.62 (1.58–4.35)
Used PHT at some time [3)]	16	8	2.05 (1.26–3.35)

1) Reference group: non-interested
2) Excluding missing values, interested n = 90 (40%), non-interested n = 143 (26%), see Methods
3) Including missing values in the denominator

dividing weight in kilograms by the square of height in meters.

Women's opinions on the menopause were elicited using the statements: "The menopause is a normal phase in a woman's life, and usually it does not need treatment by a doctor", and "A woman does not loose her femininity during the menopause". Women's opinions concerning PHT were elicited using the statements: "PHT effectively prevents osteoporosis ", "PHT should be given to all middle-aged women with (menopausal) symptoms", and "PHT should be given to most postmenopausal women". The possible answers were: I totally agree, I agree somewhat, I don't know, I disagree somewhat, and I totally disagree. In the analyses, the choices "I totally agree" and "I agree somewhat " were later combined to "agree".

After the previous statements came the remark 'the next questions deal with the menopause and PHT use. Those with normal periods and who do not use PHT may stop here'. This mistake resulted in our many missing answers concerning PHT use (see Table 2), and the percentages in Table 2 are given in two ways.

Open-ended questions were also used to ask women what kind of positive and negative features they associated with the menopause. The proportions giving positive or negative aspects are also reported in this article.

Testing the statistical significance of medians was done using Mann-Whitney's U test. Age-adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated by logistic regression, using interested women as the reference group. SAS 8.0 was used in the analyses.

Results

Altogether 2000 questionnaires were sent and after two reminders, 1312 women (66%) responded (Table 1). Non-respondent women were somewhat older and were

Table 3: Comparison of health habits and health of women interested and non-interested in participating in a randomized PHT preventive trial in Estonia, proportion (%) of women, and age-adjusted odds-ratios (OR).

	Interested (n = 225) %	Non-interested (n = 553) %	OR (95% CI) [1]
Daily smoker	18	14	0.87 (0.56–1.34)
No alcohol	13	20	1.40 (0.88–2.20)
Plenty of exercise in leisure-time	25	28	1.13 (0.78–1.62)
BMI 25–29.9 [2]	55	59	0.96 (0.69–1.34)
BMI ≥ 30 [2]	26	21	0.68 (0.47–0.99)
Current health good	24	24	1.27 (0.87–1.86)
Some chronic disease	73	67	0.70 (0.49–1.00)
Tiredness	50	45	0.83 (0.60–1.15)
Irritability	29	23	0.80 (0.56–1.16)
Depression	26	19	0.65 (0.45–0.96)
Headache	36	32	0.96 (0.68–1.34)
Sweating	32	27	0.78 (0.55–1.11)
Hot flashes	28	22	0.74 (0.51–1.07)
Sleeplessness	26	20	0.67 (0.46–0.97)
No symptoms	2	9	4.04 (1.57–10.44)

1) Reference group: "interested"
2) kg/m^2

somewhat more often residents of the capital than were respondents.

Of the 1312 respondents, 17% wanted to participate in the trial. Using the whole sample of 2000 women as a basis for calculation, 11% were interested in participating in the trial, 42% did not want to participate,12% wanted to receive more information before deciding, and 28% gave no answer ('do not know'). (Table 1).

The socioeconomic background characteristics of these four groups were very similar, but women in the "do not know" and "non-interested" groups were older than interested women. After adjustment for age, it was found that fewer non-interested than interested women had given birth. When the women who had given a clearly positive or negative answer to the question concerning their interest in participating were compared, it was found that interested women had had more contacts with the health-care system – as measured by visits to a physician and a gynaecologist during the previous year – than had non-interested women. (Table 2). Interested women had also used calcium drugs more often, and they more often reported using PHT at some time than did non-interested women.

Health habits, smoking, alcohol use, and exercise did not vary by interest in participating (Table 3). In both groups, more than half were mildly overweight, but heavy overweight was somewhat more prevalent in those interested. Interested women more often had some chronic disease, such as hypertension, cardiac failure or diabetes. (Table 3). There was no difference in regard to subjective current health, or in the proportion of women who had experienced hot flashes, but interested women more frequently reported depression and sleeplessness.

Fewer women who were interested in participating in the trial agreed that the menopause is a normal phase, and more gave negative aspects of the menopause than did non-interested women (Table 4). A more favourable opinion of PHT was held by interested than by non-interested respondents.

The "want more information" group was similar to the group of interested women in regard to the variables studied, but they had had fewer gynaecologist appointments in the last 12 months (40% vs. 53%). The "do not know" group exhibited a clearly greater difference from interested women: fewer of them had ever made use of PHT and calcium drugs; they suffered less from irritability, depression, joint pain, sleeplessness, sweating and hot flashes; they had had fewer appointments with gynaecologists because of menopausal symptoms; and they reported fewer both positive and negative aspects of the menopause.

Discussion

In the case of many background characteristics, the interested and non-interested women were similar to each other, or the differences between them were small. The

Table 4: Comparison of opinions on aging and attitudes to PHT of women interested and non-interested in participating in a randomized PHT preventive trial in Estonia, proportion (%) of women, and age-adjusted odds-ratios (OR).[1)]

	Interested (n = 225) %	Non-interested (n = 553) %	OR (95% CI) [2)]
Menopause is a normal phase	46	56	0.68 (0.50–0.94)
Women do not loose femininity in menopause	52	51	1.01 (0.73–1.39)
PHT prevents osteoporosis	27	9	4.27 (2.75–6.64)
PHT should be given to all women with symptoms	32	12	3.20 (2.16–4.74)
PHT should be given to all postmenopausal women	17	3	5.88 (3.18–10.88)
Gave positive aspects of menopause	20	17	1.38 (0.92–2.08)
Gave negative aspects of menopause	39	28	1.82 (1.30–2.57)

1) Missing values excluded from the denominator. The proportion of missing values varied from 17 to 21% in the "interested" group, and from 23 to 26% in the "non-interested" group.
2) Reference group: "non-interested"

major differences between them were in age, health, use of health services, experience and attitude towards the menopause. When compared to non-interested respondents, interested women were younger, and they suffered from poorer health in terms of chronic diseases, more reported symptoms, and more visits to a physician. Interested women had more negative experiences with the menopause and a more positive attitude to PHT, and they had also more often used PHT than had non-interested women.

As in previous preventive trials, the interested women were younger than those who were not interested [1]. But in contrast to Britton et al. [1], who found that interested women had a more healthy lifestyle, we did not find differences in health habits – except with regard to overweight. The use of health services positively correlated with women's willingness to join this trial. It seems that women's contacts to health services may increase their willingness to join a trial; or use of health services may result from their poorer health: interested women had more chronic diseases and more symptoms. Or women expected some benefits from the trial. In an imaginary trial of PHT, the advantages that the women expected from the treatment was more important than how benefits were described [16].

Interested women's negative experiences with the menopause and positive attitude to PHT, as well as a positive attitude towards PHT on the part of gynaecologists [17], may have influenced women's interest in the PHT trial. By contrast, a fifth of the respondents had no opinion concerning PHT. Its use is still infrequent in Estonia, and knowledge of PHT is likely to have been scant.

A limitation for generalizing the study results may result from our particular trial design and target group. However, the trial design of blind and non-blind groups was not presented in the invitation letter. Women were not told at this stage of the recruitment which group they would be assigned to, however, they were told of the chance to receive either hormone, placebo or no treatment. This trial concerned only mid-aged women, and different factors may influence men, or young and old people. The instruction to stop filling in the questionnaire if the women had regular menstruation and no use for hormone therapy resulted in mainly postmenopausal women being included in this report; PHT use in Estonia was low at the time of the questionnaire.

When one is recruiting participants for a randomized controlled trial, more information should be obtained from those who do not enter the trial. Ellenberg [18] argues that information involving the selection process should be obtained at each stage of selection, beginning with the screening of potential participants and proceeding to the final enrolment of those who agree to take part. This process may establish some basis for judging limits when one is generalizing results of an intervention trial. In the present population-based study, the characteristics of persons who did not return the questionnaire remain largely unknown. We know that they were somewhat older and

were more often residents of the capital than were those who were interested in joining the trial. Only 52% of people living in the capital have Estonian as their home language, and language problems in this area may explain the lower response rate to our Estonian-language questionnaires.

This preventive randomized controlled trial differed from previous preventive trials in that interested women had more chronic diseases and symptoms. In this respect they were more similar to the participants of treatment trials, in which interested persons tend to be sicker rather than more interested. Possibly some women did not regard our trial as a preventive trial but wished for better care or treatment than they would receive outside the trial – as is the case in treatment trials [3]

List of abbreviations used

Estonian Postmenopausal Hormone Therapy trial EPHT trial

Postmenopausal hormone therapy PHT

Randomized controlled trial RCT

Women's International Study of long-Duration Oestrogen after Menopause WISDOM

Odds ratio OR

Confidence Interval CI

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

SLH participated in the design and the conducting of the study, acquired and analysed the data, and drafted the manuscript; MH participated in the trial design and gave critical comments on the manuscript; PV participated in the study design; MR participated in the study design and acquisition of the data; EH conceived the study and participated in its design, participated in the acquisition of the data and gave critical comments on the manuscript. All authors read and approved the final manuscript.

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Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy

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Abstract

Purpose: To compare the effect of blind design (active drug and placebo) and nonblind design (active drug and no treatment) on recruitment.

Setting: A primary prevention trial with postmenopausal hormone therapy in Estonia.

Methods: Women who were eligible and willing to participate on the basis of the questionnaire survey were randomized into blind and nonblind groups. Recruitment rates are based on record keeping, and reasons for participating were requested in the first-year follow-up.

Results: The recruitment was 30% higher in the nonblind group: of the 4,295 women invited, 37% (95% confidence interval CI = 35–39%) in the blind group and 48% (95% CI = 46–49%) in the nonblind group were recruited. In both groups, once randomized, most of the losses were women who did not attend the first clinical examination: 49% (blind; 95% CI = 47–51%) and 40% (nonblind; 95% CI = 38–42%). The rest were found ineligible or lost their interest during clinical examinations. The reasons for joining the trial were relatively similar in the two groups.

Conclusions: Blinding decreased women's interest in joining a long-term preventive trial. Women's reasons for joining the trial were not influenced by blinding.

Keywords: Prevention trial; Recruitment; @@@Blinding; Hormone therapy

1. Introduction

There is extensive literature on barriers discouraging physicians and patients from participating in randomized trials (e.g., [1–6]). Barriers for physicians include time constraints, worry over the doctor–patient relationship, loss of professional autonomy, and difficulties with informed consent procedures. Barriers for patients include preferences for assured treatment, worry caused by uncertainty, and informed consent. We have found no previous empirical research on the influence of blinding specifically on recruitment, but preliminary results have been presented of a secondary prevention trial of osteoporotic fractures (McPherson G, Avenell A, Grant AM, McGee M, Campbell MK, McGee MA. Is recruitment easier with an open rather than a blinded, placebo-controlled design? A randomised controlled trial. Paper presented at the International Society of Technology Assessment in Health Care [ISTAHC] conference in Canmore, Canada, June 22–25, 2003). A trial in homeopathy studying the influence on blinding on outcome is being planned [7].

Blinding in trials is used for many reasons. These include the wish to minimize the bias involved in observing and recording outcomes and to eliminate outcomes resulting from beliefs, expectations, and changes in caregiver and patient behavior due to the therapy [8]. The first aim is noncontroversial—but research aimed at providing information on effectiveness in real-life situations and on changes resulting from beliefs, expectations, and behavior might usefully be included in evaluation [9]. Blinding, especially if it includes use of placebo, may negatively influence the process and feasibility of trials. The effects on feasibility may be especially important in long-term preventive drug

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trials. In such trials, participants are usually healthy and may be more difficult to motivate than are patients looking for a treatment. Furthermore, the use of the trial drug may influence other (preventive) behaviors. Compared to treatment trials, in preventive trials physicians may also be less enthusiastic about including study participants.

In a primary prevention trial with postmenopausal hormone therapy (PHT; also known as hormone replacement therapy, HRT), we wanted to study the effect on numbers recruited and the process of recruitment when using blinding (the blind group) as compared to the situation when both the caregiver and the woman will know in which arm the woman is (the nonblind group). Our hypothesis was that more women would be recruited in the nonblind group. The influence on treatment compliance and outcomes will be studied separately after the data are available.

2. Methods

The data come from the recruitment process for the Estonian Postmenopausal Hormone Therapy Trial and from the one-year follow-up. It is a randomized trial concerning the health, social, and health-services effects of PHT. Recruitment for the trial was conducted by means of a questionnaire sent to all 50- to 64-year-old (45–64, in the pilot) Estonian-speaking women in two areas, Tallinn and Tartu and their surrounding counties, in 1998 and 1999 (n = 39,713) (Fig. 1). Names and addresses were obtained from a population register; age refers to that in March 1999 (January 1998, in the pilot). The trial design was tested in two pilot studies and was modified after the first pilot in 1999. The pilot-study women (339 randomized) are included in this report because their results on recruitment were the same as in the main trial. In addition to the two pilots, seven rounds of recruitment were made in 1999 to 2001.

Attached to the recruitment questionnaire was a two-page leaflet describing the need for the trial and the assumed and known beneficial and harmful effects of PHT. The trial design was described in general terms, without mention of blind and nonblind grouping, but saying that those interested would be randomly allocated into three groups: hormone therapy, placebo, no treatment. The questionnaire asked about women's health, background characteristics, their interest in joining the trial ("Do you want to participate in a trial on postmenopausal therapy as described in the enclosed leaflet?"), and which of the local clinics they would like to attend. Interested women who were found to be ineligible on the basis of questionnaire data were sent a thank-you letter stating the reasons for their ineligibility.

The interested and potentially eligible women (n = 4,295) were randomized into four treatment arms (blind group with options PHT or placebo and nonblind group with options PHT or no therapy; the last is called the control) by clinic (three clinics), using a computer-based stratified block randomization program (block size 16). The code was sealed

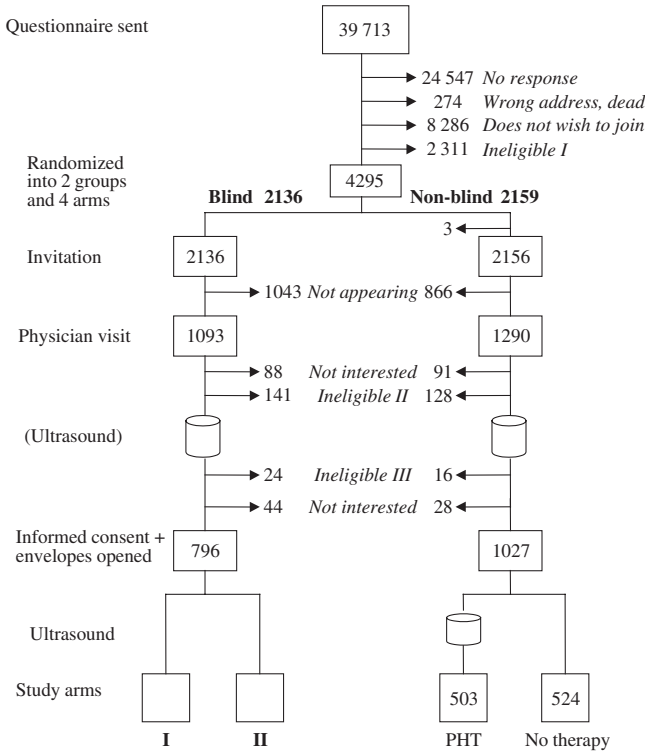

Fig. 1. Recruitment of 50- to 64-year-old Estonian women for a prevention trial with postmenopausal hormone therapy (PHT), by blind and nonblind group, numbers of women. In the nonblind arm, three women were found ineligible after randomization and were not invited.

in a fully opaque envelope with the woman's name, study number, and group (blind, nonblind) on it and stored at the clinic that she had chosen. Each woman was sent an invitation letter describing the group that she was in (i.e., blind or nonblind), and asked to make an appointment for a physician's examination. Except for the descriptions of the groups, this letter was same for the two groups. The existence of the other group was no longer mentioned. The letter was practically oriented, giving details on (a) how to make the appointment, (b) what would happen during the examination, (c) informed consent procedure and data use by the researchers, (d) obtaining and using study drugs, (e) how follow-up would occur, and (f) what women should do if they stopped taking their drugs (or started PHT, in the no-therapy arm of the nonblind group).

To make an appointment for a physician's clinical examination, the letter advised the woman to telephone a study midwife at the clinic. At each clinic, one or two service midwives were specially trained and their salary was in part paid by the project. In addition to reserving the appointment time, the midwives provided further information on the trial, which many women requested. If the woman invited did not visit the clinic, a coordinating study physician invited her by phone. Starting with the third recruitment round, if the woman had not been reached by phone, a reminder letter was sent asking her to make an appointment.

When the woman arrived at the clinic, the examining physician (one of eight) knew which group she was in (blind or nonblind), but not which arm. The physicians were employees of the clinic, but were trained for the trial and paid according to the number of women examined. They had been given detailed instructions on what to ask and measure, and what were the exclusion criteria (including current or previous breast or uterine cancer, any other cancer less than 5 years ago, history of deep vein thrombosis, pulmonary embolism, cerebral infarction, meningioma, porphyria, endometriosis, myocardial infarction less than 6 months ago, liver function disorders or hepatitis less than 3 months ago, untreated hypertension or hypertension resistant to drug therapy, irregular postmenopausal bleeding, abnormal PAP-screen result, menstrual bleeding within the last 12 months, desire for PHT, or plans to move out of the area). Gynecological ultrasound examination was offered in the blind group to all women with uterus or ovaries intact, and in the nonblind group to most women.

Determining eligibility required two visits to the clinic, because results of some examinations were not ready at the first visit. After the physician found a woman eligible, her consent was requested (in writing) and the envelope containing the code for the treatment arm was opened; once the envelope was opened, the woman was included into the trial. At the very beginning, some physicians misunderstood the instructions and some envelopes were opened before the informed consent; this was soon corrected, however, and only 12 such women (0.7%) were included into the trial. The envelope contained a drug sheet for the midwife and a one-page leaflet to be given to the woman. This leaflet again explained the study design and the method of taking or not taking the drug, and described potential adverse effects and any symptoms that would necessitate contacting the study physician or an emergency clinic. The drug sheet contained the code for the drug bottle and technical information for the midwife, who stored the sheet for her use. Women in the PHT arm of the nonblind group who had not yet received gynecological ultrasound scanning were offered it after the envelope was opened. (Women who showed an abnormal result were retained in the trial, but did not receive drugs.) Women were taught how to palpate their breasts to look for breast tumors.

During visits to the physician, some eligible women lost interest in the trial. If this occurred before the envelope was opened, the woman in question was excluded from the trial. If it occurred after the envelope was opened, she was included and followed through registers and annual questionnaires.

The drug used was a fixed combination of conjugated equine estrogens 0.625 mg and medroxyprogesterone acetate (MPA) (Prempro; Wyeth-Ayerst, Philadelphia, PA, USA), taken daily. The MPA dose was 5 mg for women whose last menstrual period had occurred less than three years ago, and 2.5 mg for the rest. In the blind group, the drug bottles were marked with a code; in the nonblind group, the name of the drug also appeared on the bottle. The women received a seven-month supply of drug bottles, and they were asked to come to the midwife's reception for the next seven-month supply.

A year after recruitment, the women were sent a questionnaire asking about their health and their feelings concerning the trial. Women in the blind group and PHT women in the nonblind group were reminded to make an appointment for their physician's examination held one year later. (At the time of writing, data from the first seven recruitment rounds were available; $n = 1{,}516$ and 1,099 responding.) In the blind group, 73% responded; in the nonblind group, the figure was 72%.

Before the trial started—and once during the recruitment, in May 2000—the researchers described the trial in local newspapers and on television, to increase women's awareness of the trial and interest in its purpose. The trial was approved by the Committee of Medical Ethics in Tallinn, Estonia, and by the ethics committee at the University of Tampere, Finland.

3. Results

3.1. Numbers recruited

Figure 1 shows the recruitment into the trial. Overall, the proportion of women interested in joining the trial was relatively high: 6,605 women expressed interest (17% of those to whom an invitation was sent and 44% of those responding). On the basis of the questionnaire data, one third (35%) of the 6,605 women interested were judged ineligible, mainly on the basis of health or because they had menstruated within the past 12 months. This left 4,295 willing and eligible women (11% of the 39,713 women approached).

After receiving the invitation letter specifying their study group, fewer women in the blind group (51%) than in the nonblind group (60%) came to the physician's examination (Table 1; Fig. 1). During the examination, physicians defined rather more women in the blind group as ineligible, and rather more women changed their minds and did not want to join the trial than in the nonblind group. In the nonblind group, the final recruitment rate was 30% higher than in the blind group; the net difference between the groups was 10.3% (95% confidence interval CI = 7.4–13.2%).

In the original study protocol, ultrasound examination of the uterus in the nonblind group was to be made only in the PHT arm and only after the envelope had been opened; however, physicians wanted to provide a clinical service for the women, and most women in the nonblind group were examined before the opening of the envelope.

Exclusions made by physicians during the initial examination were obtained from their study records. The number of women excluded ($n = 309$) was larger than the number of women with predetermined reasons for exclusions ($n = 86$). Other health problems were commonly recorded and sometimes, in the judgment of the physicians, also merited exclusion. There were no major differences between the two

Table 1
Recruitment by blind and nonblind groups for postmenopausal hormone therapy

	Blind		Nonblind		Difference between blind and nonblind group		
	n	%	*n*	%	%	95% CI	*P*
Randomized	2,136		2,159				
Attended physician's examination[a]	1,093	51	1,290	60	8.6	5.6, 11.5	<0.001
Found ineligible[b]	165	15	144	11	3.9	1.2, 6.7	<0.001
Not interested[b]	132	12	119	9	2.9	0.4, 5.3	0.002
Recruited (envelopes opened)[a]	796	37	1,027	48	10.3	7.4, 13.2	<0.001

[a] % calculated from those randomized.
[b] % calculated from those attending physician's examination (1,093 and 1,290).

groups in the numbers excluded for such additional health reasons. In the blind group, 41 women had ailments listed in the exclusion list; the figure for the nonblind group was 45.

3.2. Reasons for joining the trial

In the follow-up questionnaire sent one year later to the first 1,516 women, the reasons for joining the trial, given retrospectively, were relatively similar in the two groups; in the nonblind group, women in the two arms also gave fairly similar reasons (Table 2). Of the alternatives provided, women chose reasons that benefited them personally as well as reasons that were 'good' in general. The most common reasons given were the opportunity to obtain the medical examination by the trial physician and the facilitation of Estonian research. "Free drugs" was chosen by only a very few respondents. In the nonblind group, the women in the control group chose the annual physician's examination more often and help in the menopause less often than was the case with the women receiving PHT.

When asked what attitude their partners had towards their participation in the trial, the women in the both groups reported similarly: most partners either agreed with their participation (52% of women, excluding those without a partner) or did not care (34%). Some women (14%) had not informed their partners.

There was no difference between the two groups in women's satisfaction with the information provided by the study midwife (67% had received enough information) or the physician (81%) or with that found in the leaflet (76%). The rest said that they had not received enough information in general or that more attention should have been paid to some particular aspect. The question did not differentiate between information on the trial, the menopause, or drugs but asked only about "information in which you were interested." Equally many women (7% in the blind and 8% in the nonblind group, difference 1.9% ; 95% CI = −1.2% to 5.0%) had suggestions on ways of improving the trial.

In the survey, the women in the two groups reported differently with regard the arm to which they had (before entering the trial) wished to be assigned (Table 3). Women in the blind group and PHT women in the nonblind group most often reported that they had hoped to end up in the PHT arm or that they had no preference. By contrast, control women in the nonblind group more often reported that they would have liked to end up in the arm receiving nothing.

4. Discussion

As expected, compared to the blind group, more women joined our preventive randomized trial when they were going to know, after inclusion, to which treatment arm they belonged. Most of this difference was explained by the

Table 2
Women's reasons for joining the trial as reported in the follow-up survey after one year[a]

		Nonblind				Difference between blind and nonblind groups		
	Blind (n = 477), %	PHT (n = 300), %	Control (n = 322), %	Total (n = 622), %	Total (N = 1,099),	%	95% CI	*P*
Altruistic								
Facilitate research	39	36	37	37	37	1.9	−3.9, 7.7	0.5
Help future women	18	23	19	21	19	3.3	−1.4, 8.0	0.2
Egoistic								
Physician's examination	42	42	58[b]	50	46	8.1	2.2, 14.0	0.008
Help in menopause	36	36	22[b]	29	32	7.3	1.7, 12.9	0.01
Better health care	9	11	11	11	10	2.3	−1.3, 5.8	0.2
Better access	5	5	6	5	5	0.1	−2.6, 2.7	1.0
Free drugs	5	6	5	5	5	0.5	−2.1, 3.1	0.7
Other	6	8	5	6	6	0.6	−2.2, 3.4	0.7

Abbreviations: PHT, postmenopausal hormone therapy.
[a] The first 1,099 respondents. Women could choose several alternatives. Reasons are compared between the blind and nonblind group, and within the nonblind group between the PHT and control groups.
[b] The difference between the PHT and the Control arms is statistically significant ($P < .001$).

Table 3
Women's preference for the treatment arm before joining the trial, as reported in the follow-up survey after one year[a]

		Nonblind			
	Blind (n = 477), %	PHT (n = 303), %	Control (n = 319), %	Total (n = 622), %	Total (N = 1,099), %
Hormone treatment	41	49	21	34	37
Nonhormone arm	13	12	37	25	19
No preference	38	33	35	34	36
Do not remember or No information	8	7	7	7	7
Total	100	100	100	100	100

The differences in the distribution of preferences between the blind and nonblind group and between the PHT and the control arm are statistically significant ($P < .001$) according to a X^2-test including all rows.

Abbreviations: PHT, postmenopausal hormone therapy.

[a] The first 1,099 respondents.

women's own choice; the varying exclusions by physicians explained less. For every 100 women entered into the nonblind trial, we may predict that 20 would not have joined a blinded trial. Of these, 17 would not have attended for physician assessment, 2 would have been found ineligible, and 1 would have declined consent after assessment. Women's reasons for joining the trial, as recalled a year later, were relatively similar in the two groups, and thus the reasons for varying interest could not be ascertained on the basis of our data. The 'no-therapy' women in the nonblind group, however, more often gave a physician's examination as a reason for joining the trial than did other women. This is the only extra benefit that they received from the trial, which may have distorted their memory of their original expectations.

Over half of the women reported that prior to the trial they had had a preference for a particular arm. In the blind group and in the PHT arm, it was usually the active drug treatment arm. In the no-therapy arm, more women reported they had wanted to end up in the nontreatment arm. Clearly, this reflects the fact that the one-year of experience had distorted pretrial opinions. The finding that people tend to be happy with the treatment that they receive is in accordance with previous literature [10–12].

Why were women more willing to join a nonblind study than a blind study? Our intuition suggests that it is easier to contemplate a long-term trial if informed of the treatment one will be receiving. This is especially true in the case of a treatment such as PHT, which (unlike vitamins or cholesterol-lowering drugs) frequently has immediate effects. Furthermore, the use of placebo may be an alienating factor. In a British study investigating (in a hypothetical situation) the feasibility of doing a trial with hormone therapy, more women said they would be willing to join a trial comparing two active drugs than a trial comparing two active drugs and a placebo [13].

At the time of the recruitment, Estonian gynecologists had a positive opinion of PHT [14]. We did not systematically study the opinions of our eight study physicians. Our impression is that also they had positive opinions of PHT, but were worried over contraindications. We may hypothesize that when physicians were in doubt concerning the eligibility of a woman, they may have felt safer about including the woman when the medication would be known.

Do our results apply in other contexts, in other health problems or other populations? We found only one earlier study; it asked the same question in a secondary prevention trial of osteoporotic fractures among older Scottish people (McPherson G, Avenell A, Grant AM, McGee M, Campbell MK, McGee MA. Is recruitment easier with an open rather than a blinded, placebo-controlled design? A randomized controlled trial. Paper presented at the International Society of Technology Assessment in Health Care [ISTAHC] conference in Canmore, Canada, June 22–25, 2003). Their results were similar: people with a history of osteoporotic fractures were more likely to consent to a randomized trial with an open design than to one with a blind design. Common thinking suggests that people would prefer to know what they take, even in a trial; however, that desire may be much smaller in situations in which the condition is serious, some treatment is necessary, and the study duration is short. Because the question of recruitment success and the importance of blinding are crucial for trials, this issue should be further studied.

If the sole purpose of our trial had been to study the recruitment success, the ideal would have been to randomize from the beginning (i.e., all 39,713 women). Based on other studies, however, we rightly expected that only a minority of women would be interested in joining the trial. Randomization into blind and nonblind from the beginning would, for logistic reasons, have been more expensive. Because the general knowledge of laypeople of blinding and placebos is generally poor, and our first letter did not yet properly explain them, we do not think that the possibility of being included into a blind or nonblind group was a major determinant in expressing the initial interest.

The influence on numbers is important in terms of feasibility (many trials suffer from fewer patients than expected) [4,6,15]. In this trial, nonblinding was useful in increasing the total number of women in the study. One may hypothesize that the higher the participation rate is, the better

the participants represent the target population. In this study, in both groups only a proportion of women who were approached and were eligible joined the trial. Thus, allowing subjects to know their treatment (after trial inclusion) did not improve the generalizability to our target population, mid-aged healthy Estonian women.

How much the effects of treatment depend on patient characteristics correlating to interest to join a trial is unknown in most trials [16]. A comparison of the women who in our original recruitment questionnaire said they were or were not interested in joining the trial showed that interested women were younger and had had more contact with health care (indicated by having more often had children, visits to a physician in the past year, and use of calcium); sociodemographic characteristics or health habits did not explain the interest (S.-L. Hovi, STAKES, unpublished data, 2003). Whether these differences and those created by later loss of interest relate to hormone therapy effects is unknown. The importance of obtaining a representative sample of the target population in the case of PHT remains speculative. A review by Britton et al. [17] suggests that selective participation may exaggerate effects in treatment trials, but may lead to underestimation in the case of prevention trials. Representative samples are possible in trials studying problems for which some treatment is needed or expected, and in which the informed consent is requested after inclusion in the study (e.g., [1,18,19]).

The duration of the PHT in our trial was originally planned for five years. As suggested by other trials on PHT [20] and length of PHT in normal practice [21–24], we assume that many women will drop out of the therapy before the end of the trial. This will dilute the effects. We will later study whether dropouts will be similar in the two arms, and especially whether treatment compliance will weaken or strengthen the superiority of the nonblind design for study power. Likewise, the strengths and weaknesses of the two groups in measuring different outcomes will be studied later. These comparisons are likely to illuminate the benefits of blinding.

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Experiences of a long-term prevention trial in a maiden environment: Estonian Postmenopausal Hormone Therapy trial

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Abstract

As preventive medications becomes popular, long-term trials are necessary to show their effectiveness, often using a licensed drug. A trial of longer duration will bring more demands to a study. Very few reports have described what happens in long-term trials and the process in practice; it has remained something of a black box. The purpose of this article 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, health service use, and also the effect of blinding on recruitment and results. The data of this report comes from written material such as notes from and minutes of 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. Estonia changed rapidly during the trial period (1998 to 2004): continually developing legislation and organizational changes demanded constant actions, but newly emerging technology made everyday management of the trial easier. Significant results from other trials involving hormone therapy compelled us to change the trial protocol, and the EPHT was stopped earlier than planned. Reports detailing with these kinds of changes are necessary for at least two reasons: First to add generalisability to the results, with preferably structured reports being given as part of research results, and secondly, to help future trials to anticipate possible changes.

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