The Women’s International Study of long Duration Oestrogen after Menopause (WISDOM) was the world’s only remaining trial, and perhaps the last chance, to examine the long-term effects of combined hormone replacement therapy (HRT). It was arguably the world’s largest and longest randomized, placebo-controlled trial of any therapy. In this edition, Vickers and colleagues give details of this 15-year trial which was to involve 22000 postmenopausal women being treated with placebo, estrogen alone or combined HRT for 10 years with 5 years of further follow-up. Further commentaries on the demise of WISDOM have been offered in this edition by Dr Beverley Lawton (WISDOM, New Zealand), Dr Paul Komesaroff (WISDOM, Melbourne) and in a letter from Dr James Fiorica who had no association with WISDOM and offers an independent view.

WISDOM was designed to look at the ‘whole woman’ and all major morbidities and mortalities occurring during the trial. It included, in particular, measurements of quality of life, cognitive function and menopausal symptoms. It had the potential to recruit younger and healthier women than those recruited in the Women’s Health Initiative (WHI) and might have better investigated the still untested hypothesis that HRT may have a primary cardioprotective role in the early postmenopausal woman, by helping to prevent atherosclerosis. Secondary prevention studies do not support a role for the treatment of established atherosclerosis and HRT may even have an early adverse effect in these circumstances. The debate about whether many of the so-called ‘healthy’ women in the WHI study could have had established atherosclerosis will go on and on, but probably WHI is a mixed primary and secondary study in terms of the prevention of cardiovascular disease. Therefore, one cannot state that the data from WHI have shown that HRT is or is not cardioprotective in women treated from menopause. It is very important that all the data from WHI becomes freely available to allow analysis of where and when events occurred. Ideally, the data should be accessible on a website. The early cessation of the combined HRT arm of WHI after 5 years means that this arm of WHI was only a medium-term trial, and that, with the withdrawal of the major funding for WISDOM, it is unlikely that there will ever be a long-term Level 1 trial of combined HRT. It is important to note that the estrogen-only arm of WHI continues and will run to 8.5 years. This should give further valuable information. As the dust settles after the unfortunate media response to the WHI data, which caused fear and ill-advised responses in many HRT users, questions are being asked about the clinical and statistical relevance of the data from this trial. Such questions include:

• Was it appropriate to have an automatic stopping point when, after multiple looks at the data, one cancer (breast) was seen to be more prevalent in the treatment group than the placebo group when there was an equal reduction in other major cancers in the treatment group?
• Was there a steeper than normal rise in the increasing prevalence of breast cancer and cardiovascular events at 5 years normally seen with age, or was the difference at that time point due to an unexpected temporary decrease in adverse events in the placebo group? Annualized percentage rates of these events suggest the latter.
• For those treated for 6–7 years, the difference in events between the placebo and treatment groups disappeared. Should this have allowed continuation of the trial to see if the difference at 5 years was spurious?
• Should the nominal or the adjusted confidence intervals be applied when multiple outcomes are being assessed and multiple looks at the data are being performed?
industry funding was generally avoided but an extra support from other countries and agencies administrative team of WISDOM had to seek Government, the ambitious and hard-working was very well funded from one source, i.e. the US increase its statistical power. Unlike WHI, which co-fund WISDOM, help with recruitment and that many other European countries would Research Council (MRC, UK). It had been hoped 10 years ago by a forward thinking Medical increase or weight may have compromised this research and these important long-term outcomes cannot now be adequately assessed (see the Letter in this issue8). In the June 2002 edition of Climacteric, we published a review of the methodologies of the sub-studies in WHI and WISDOM, designed to look at cognitive aging and dementia risk in postmenopausal women7. The early cessation of a major arm of WHI and the withdrawal of funding for WISDOM have compromised this research and therefore long-term outcomes cannot be adequately assessed (see the Letter in this issue8). Climacteric would welcome comment from the investigators involved in WHI on the above points in future issues.

WISDOM was partly funded and set up over 10 years ago by a forward thinking Medical Research Council (MRC, UK). It had been hoped that many other European countries would co-fund WISDOM, help with recruitment and increase its statistical power. Unlike WHI, which was very well funded from one source, i.e. the US Government, the ambitious and hard-working administrative team of WISDOM had to seek extra support from other countries and agencies before the trial could begin. Pharmaceutical industry funding was generally avoided but an HRT product was needed to be assessed. The only pharmaceutical company that offered its product for assessment was Wyeth. Its product Premarin is not widely used in Europe and this may have contributed to a lack of support from European researchers and funders. However, Australian and New Zealand researchers and funders saw the importance of WISDOM and joined the trial in 2002. Co-funding in Australia was obtained from NH&MRC, The National Heart Foundation, The Anti-Cancer Foundation, the Australian Menopause Society and RANZCOG. Using a different technique of enrolment, where women were invited by their general practitioners to group information sessions run by the researchers, and where the trial was explained in detail, Australian recruitment quickly met its target. Later, Australia and New Zealand, which was also recruiting successfully, were further funded by the MRC to increase their numbers to make up for slow recruitment in the UK, where 5664 women had been randomized. Australia and New Zealand were to contribute 3590 patients for a final total of 22 000 by the end of 2003. This target seemed feasible.

The slow funding and co-funding of WISDOM meant that WHI had a 5-year start using a similar treatment and protocol. This made WISDOM vulnerable to early reporting by WHI of adverse or beneficial results. Although there was a benefit in both trials studying the same therapeutic regimen, as this would allow combination of results, there was an inherent weakness that only one regimen and one route were being tested and that early results or methodological issues in WHI might influence the running of WISDOM. Another possible lesson, for those seeking long-term funding for clinical trials, is to keep the funders motivated when such large amounts of money are involved and there is the potential for the funding administration to change. At the set up of WISDOM, the MRC (UK) requested and obtained very detailed analysis of the project from over 20 international referees. Lobbying about the importance of this project to women’s health was strong. However, did lobbying subside after funding was allocated and did the administration, corporate memory and funding priorities of the MRC (UK) change? After the sudden publication of the early WHI results in July 2002, the MRC (UK) appropriately called a temporary moratorium on WISDOM. WISDOM’s data monitoring committee assessed its early results and reported that it was ethically and scientifically appropriate for WISDOM to

When adjusted confidence intervals reach unity, is it statistically significant?

Was not the hazard ratio for breast cancer of 1.26 in WHI half the relative risk of 1.53 described in the re-analysis of previous observational trials?

Was WHI a mixed primary and secondary cardiovascular prevention study which could not test the hypothesis that HRT may be cardioprotective when started around menopause?

If combined HRT promotes existing undetected breast cancers, would any increase have stayed constant after 5 years or, if it caused breast cancer, would the increase have been exponential and outweighed any benefits and thus stopped the trial in later years?

Would the decrease in fractures seen as early as 5 years have increased exponentially as length of therapy and risk with age increased? Thus, the extent of further benefit at 10 years is unknown and potentially underestimated.

What would have been the effects of long-term HRT on cognitive function and dementia? A recent report of women using HRT for more than 10 years has shown an associated reduction in Alzheimer’s disease (odds ratio 0.31, confidence interval 0.17–0.86)6. In the June 2002 edition of Climacteric, we published a review of the methodologies of the sub-studies in WHI and WISDOM, designed to look at cognitive aging and dementia risk in postmenopausal women7. The early cessation of a major arm of WHI and the withdrawal of funding for WISDOM have compromised this research and therefore long-term outcomes cannot now be adequately assessed (see the Letter in this issue8). Climacteric would welcome comment from the investigators involved in WHI on the above points in future issues.

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continue. The steering committee of WISDOM endorsed this recommendation after assessment of the available data from WHI. However, the MRC (UK) called for an urgent separate report from an international committee of its choice. The WISDOM (UK) team had little time to justify the continuation of WISDOM and WISDOM (Australia) and WISDOM (New Zealand) were not invited to contribute to the advisory committee’s deliberations or the MRC decision. In October 2002, the MRC (UK) decided to withdraw funding ‘for scientific and practical reasons’. It stressed that there were no safety concerns for the women in WISDOM, but it cited the findings of WHI as the main influence for its decision. The MRC media release said that their independent advisory committee, which had many epidemiologists but few clinicians working in menopausal medicine, had advised that the results of the trial would not be available for another decade and would be unlikely to influence clinical practice.

Of course, it is the absolute right of funders to withhold funding for any trial, but many might have argued that WISDOM was a long-term trial and it was known from the beginning that it would take 10–15 years to obtain results. Many would also argue that WISDOM was obtaining clinical data that probably would indeed have influenced clinical practice, as it was looking at quality of life, menopausal symptom control, cognitive function, dementia, eye and dental health, arthritis, all cancers and the influence of HRT on vascular disease in younger postmenopausal women, etc. Sadly, the influence of long-term combined HRT on these outcomes will probably never be known accurately without Level 1 trials, which may now never be conducted, given the cost and the politics of such a trial. Governments may need to see the potential for economic gain rather than improved quality of life.

Clinicians can now only advise women of the possible mixed risks and benefits of HRT after 5 years of use and let them decide whether they derive any increase in quality of life on longer-term HRT. HRT also remains one evidence-based option for the long-term prevention and treatment of osteoporosis when fully informed consent is obtained and the choice of HRT and other therapeutic options is tailored to the individual. Without long-term trials, HRT cannot be advocated for the prevention of other chronic conditions.

Women are already conducting their own unrandomized, uncontrolled and unpublished trials of long-term HRT, as evidenced by the mean length of use of 12.3 years of HRT in Australian women over age 70, as reported in this issue. Currently, women are advised to try going off HRT after 5 years, but many choose to return to HRT because they perceive a benefit. It is important to inform them of (and document) the currently known risks of HRT, and a new independent video is available to help clinicians with this task (see p. 410). Without randomized, controlled trials to assess the risks/benefits/cost ratio of long-term combined HRT, we shall be left with the limited data from WHI on one regimen and one route, together with the data from observational trials. One such observational trial of combined HRT and breast cancer by de Lignieres and colleagues is published in this issue. Its results are reassuring and conclude that early interruption of combined HRT is not justified where benefits are perceived.

The debate about prescribing combined HRT longer than 5 years, estrogen alone, other HRT regimens and routes and other outcomes not reported in WHI will continue now, without strong data for years and without WISDOM! The closure of this trial is a sad loss for women and the future health of our daughters. We have let them down!

Potential conflict of interest
Professor MacLennan was Chairman of WISDOM Australia and Dr Sturdee was a member of the WISDOM Steering Committee.

References
2. Lawton BA, Rose SB, Dowell AC. Cessation of the WHI and WISDOM trials: a New Zealand perspective [Comment]. Climacteric 2002;5:326–8

7. Zec RF, Trivedi MA. Effects of hormone replacement therapy on cognitive aging and dementia risk in postmenopausal women: a review of ongoing large-scale, long-term clinical trials. Climacteric 2002;5:122–34

