Menopause: diagnosis and management

NICE guideline
Draft for consultation, June 2015

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence is contained in the full version.
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Introduction

Menopause is when a woman stops having periods as she reaches the end of her natural reproductive life. This is not usually abrupt, but a gradual process during which women experience perimenopause before reaching postmenopause. The average age of menopause in the UK is 51. However, this varies widely and 1 in 100 women experience premature ovarian insufficiency.

Oestrogen depletion associated with menopause causes irregular periods and has many other effects on the body. The most common symptoms are hot flushes and night sweats. Other symptoms include mood changes, memory and concentration loss, vaginal dryness, a lack of interest in sex, headaches, and joint and muscle stiffness. Quality of life may be severely affected.

Most women (8 out of 10) experience some symptoms, typically lasting about 4 years after the last period, but continuing for up to 12 years in about 10% of women. Prolonged lack of oestrogen affects the bones and cardiovascular system and postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis.

Around a million women in the UK use treatment for their menopausal symptoms. The advice and support available is variable, and use of hormone replacement therapy (HRT) – a highly successful treatment for common symptoms of menopause – varies with socioeconomic and cultural factors. The number of prescriptions for HRT almost halved after 2 large studies, the Women’s Health Initiative (2002) and the Million Women Study (2003). However, these studies focused on the use of HRT in chronic disease prevention and potential long-term risks rather than considering the benefits in terms of symptom relief. The balance of benefits and risks of HRT use therefore has yet to be confirmed for both patients and their healthcare providers.

This guideline addresses the diagnosis and management of menopause. It covers women in the perimenopause and postmenopause, and the particular needs of women with premature ovarian insufficiency and women with
hormone-sensitive cancer (for example, breast cancer). The guideline
concentrates on the clinical management of menopause-related symptoms,
considers both pharmaceutical and non-pharmaceutical treatments, includes a
health economic analysis, and reviews the benefits and adverse effects of
HRT used for up to 5 years. It applies to all settings in which NHS services are
provided.

**Medicines**

The guideline will assume that prescribers will use a medicine’s summary of
product characteristics to inform decisions made with individual patients.
Patient-centred care

This guideline offers best practice advice on the care of menopausal women.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England — all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. If it is clear that the child or young person fully understands the treatment and does not want their family or carers to be involved, they can give their own consent. Healthcare professionals should follow the Department of Health’s advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.
Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also ‘Patient-centred care’).

Interventions that must (or must not) be used

We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a ‘strong’ recommendation

We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer…’) when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.
1 Recommendations

The following guidance is based on the best available evidence. The full guideline [hyperlink to be added for final publication] gives details of the methods and the evidence used to develop the guidance.

Terms used in this guideline

Compounded bioidentical hormones Unregulated plant-derived hormonal combinations similar or identical to human hormones that are compounded by pharmacies to the specification of the prescriber.

Fragility fracture Fractures that result from mechanical forces that would not ordinarily result in fracture (such as a fall from a standing height or less).
Reduced bone density is a major risk factor for fragility fractures, which occur most commonly in the spine, hip and wrist.

Low mood Mild depression symptoms that impair quality of life but are usually intermittent and often associated with hormonal fluctuations in perimenopause.

Menopause A biological stage in a woman's life that occurs when she stops menstruating and reaches the end of her natural reproductive life. Usually it is defined as having occurred when a woman has not had a period for 12 consecutive months (for women reaching menopause naturally). The changes associated with menopause occur when the ovaries stop functioning. Menopause occurs following the cessation of egg (oocyte) maturation and of oestrogen and progesterone secretion.

Menopausal women This includes women in perimenopause and postmenopause.

Perimenopause The time in which a woman has irregular cycles of ovulation and menstruation leading up to menopause and continuing until 12 months after her final period (also known as menopausal transition or climacteric).

Postmenopause The time after menopause has occurred, starting when a woman has not had a period for 12 consecutive months.
Premature ovarian insufficiency  Menopause occurring before the age of 40 years (also known as premature ovarian failure or premature menopause). It can occur naturally or as a result of medical or surgical treatment.

Urogenital atrophy  Thinning and shrinking of the tissues of the vulva, vagina, urethra and bladder caused by oestrogen deficiency that results in multiple symptoms such as vaginal dryness, vaginal irritation, a frequent need to urinate and urinary tract infections.

Vasomotor symptoms  Menopausal symptoms such as hot flushes and night sweats caused by constriction and dilation of blood vessels in the skin that can lead to a sudden increase in blood flow to allow heat loss.

1.1  Diagnosis of perimenopause and menopause

1.1.1 Diagnose the following without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms:

- perimenopause based on vasomotor symptoms and irregular periods
- menopause in women who have not had a period for at least 12 months
- menopause based on symptoms in women without a uterus.

1.1.2 Take into account that it can be difficult to diagnose menopause in women taking sex steroids.

1.1.3 Do not use the following laboratory and imaging tests to diagnose perimenopause or menopause in women aged over 45 years:

- anti-Müllerian hormone
- inhibin A
- inhibin B
- oestradiol
- antral follicle count
- ovarian volume.
1.1.4 Do not use a serum follicle stimulating hormone (FSH) test to diagnose menopause in women using combined oestrogen and progestogen contraception or high-dose progestogen.

1.1.5 Consider using a FSH test to diagnose menopause only:

- in women aged over 45 years with atypical symptoms
- in women aged 40 to 45 years with menopausal symptoms, including a change in their menstrual cycle
- in women aged under 40 years in whom menopause is suspected (see also section 1.5).

1.2 Information and advice

1.2.1 Give information to menopausal women and their family members or carers (as appropriate) that includes:

- an explanation of the stages of menopause
- common symptoms (see recommendation 1.2.3) and diagnosis
- lifestyle changes and interventions that could help general health and wellbeing
- the benefits and risks of treatments for menopausal symptoms.

1.2.2 Give information on menopause in different ways to help encourage women to discuss their symptoms and needs.

1.2.3 Explain to women that as well as a change in their menstrual cycle they may experience a variety of symptoms associated with menopause, including:

- vasomotor symptoms (for example, hot flushes and sweats)
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (for example, low mood)
- urogenital symptoms (for example, vaginal dryness)
- sexual difficulties (for example, low sexual desire).
1.2.4 Offer women who are likely to go through menopause as a result of medical or surgical treatment (including women with cancer, at high risk of hormone-sensitive cancer or having gynaecological surgery) support and:

- information about menopause and fertility before they have their treatment
- referral to a healthcare professional with expertise in menopause.

1.3 Managing short-term menopausal symptoms

1.3.1 Adapt a woman’s treatment based on her changing symptoms as she goes through the stages of menopause.

Vasomotor symptoms

1.3.2 Offer hormone replacement therapy (HRT) for vasomotor symptoms after discussing the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of oral or transdermal preparations as follows:

- oestrogen and progestogen to women with a uterus
- oestrogen alone to women without a uterus.

1.3.3 Do not routinely offer selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) as first-line treatment for vasomotor symptoms alone.

1.3.4 Explain to women that although there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms, their safety is unknown and different preparations may vary.

Psychological symptoms

1.3.5 Consider HRT to alleviate low mood in menopausal women.

1.3.6 Consider cognitive behavioural therapy (CBT) to alleviate low mood and anxiety in menopausal women.
1.3.7 Ensure that menopausal women and healthcare professionals involved in their care understand that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression (see the NICE guideline on depression in adults).

**Altered sexual function**

1.3.8 Consider testosterone<sup>1</sup> supplementation for menopausal women with low sexual desire if HRT alone is not effective.

**Urogenital atrophy**

1.3.9 Offer low-dose vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms.

1.3.10 If systemic HRT is contraindicated, consider low-dose vaginal oestrogen after seeking advice from a healthcare professional with expertise in menopause.

1.3.11 If low-dose vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause.

1.3.12 Explain to women with urogenital atrophy that:

- symptoms often come back when treatment is stopped
- adverse effects from low-dose vaginal oestrogen are very rare
- they should report unscheduled vaginal bleeding to their GP.

1.3.13 Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.

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<sup>1</sup>At the time of consultation (June 2015), testosterone did not have a UK marketing authorisation for this indication in women. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
1.3.14 Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy.

**Complementary therapies and unregulated preparations**

1.3.15 Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown.

1.3.16 Explain to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown.

1.3.17 Explain to women with breast cancer that St John’s wort may be a treatment option for menopausal symptoms but can interact with other medicines (for example, tamoxifen).

**Review and referral**

1.3.18 Discuss with women the importance of keeping up to date with nationally recommended health screening.

1.3.19 Review each treatment for short-term menopausal symptoms:

- at 3 months to assess efficacy and tolerability
- annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).

1.3.20 Refer women to a healthcare professional with expertise in menopause if treatments do not improve their menopausal symptoms or they have ongoing troublesome side effects.

1.3.21 For women with menopausal symptoms and contraindications to HRT:

- provide information on non-hormonal and non-pharmaceutical treatments (for example, CBT, hypnosis, acupuncture and relaxation techniques) for the relief of menopausal symptoms
- consider referral to a healthcare professional with expertise in menopause.
1.3.22 Consider referring women to a healthcare professional with expertise in menopause if there is uncertainty about the most suitable treatment options for their menopausal symptoms.

Starting and stopping HRT

1.3.23 Explain to women with a uterus that unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment but should be reported at review appointments.

1.3.24 Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment.

1.3.25 Explain to women that:

- gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term
- gradually reducing HRT may limit recurrence of symptoms in the short term.

Women with or at high risk of breast cancer

1.3.26 For advice on the treatment of menopausal symptoms in women with breast cancer or at high risk of breast cancer, see section 1.13 of the NICE guideline on early and locally advanced breast cancer and section 1.7 of the NICE guideline on familial breast cancer.

1.3.27 Offer menopausal women with or at high risk of breast cancer:

- information on all available treatment options
- referral to a healthcare professional with expertise in menopause.

1.4 Long-term benefits and risks of hormone replacement therapy

Venous thromboembolism

1.4.1 Explain to women that:
• the risk of venous thromboembolism (VTE) associated with HRT is greater for oral than transdermal preparations
• the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline risk.

1.4.2 Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30.

1.4.3 Refer menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

**Cardiovascular disease**

1.4.4 Ensure that menopausal women and healthcare professionals involved in their care understand that HRT:

• does not increase cardiovascular disease risk when started in women aged under 60 years
• does not affect the risk of dying from cardiovascular disease.

1.4.5 Be aware that cardiovascular risk factors (for example hypertension) do not automatically preclude a woman from taking HRT but should be taken into account.

1.4.6 Using tables 1 and 2, explain to women that:

• the baseline risk of coronary heart disease and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors
• HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease
• HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.
1.4.7 Explain to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. Also explain that the baseline risk of stroke in women aged under 60 years is very low (see table 2).

Table 1 Absolute rates of coronary heart disease for different types of HRT compared with no HRT (or placebo), different duration of HRT use and time since stopping HRT for menopausal women

<table>
<thead>
<tr>
<th></th>
<th>Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (baseline risk in the UK population over 7.5 years: 26.3 women per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past users</td>
</tr>
<tr>
<td>Women on oestrogen alone</td>
<td>RCT estimate(^1)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>–</td>
</tr>
<tr>
<td>Women on oestrogen plus progesterogen</td>
<td>RCT estimate(^1)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>–</td>
</tr>
<tr>
<td>Women on any HRT</td>
<td>RCT estimate</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>3 fewer (from 4 fewer to 1 fewer)</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; RCT, randomised controlled trial

\(^1\) For women aged 50–59 years

For full source references, see the full guideline
Table 2: Absolute rates of stroke for different types of HRT compared with no HRT (or placebo), different duration of HRT use and time since stopping HRT for menopausal women

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference in stroke incidence per 1000 menopausal women over 7.5 years (baseline risk in the UK population over 7.5 years: 11.3 women per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past users</td>
</tr>
<tr>
<td>Women on oestrogen alone</td>
<td>RCT estimate</td>
</tr>
<tr>
<td></td>
<td>Observational estimate</td>
</tr>
<tr>
<td>Women on oestrogen plus progestogen</td>
<td>RCT estimate</td>
</tr>
<tr>
<td></td>
<td>Observational estimate</td>
</tr>
<tr>
<td>Women on any HRT</td>
<td>RCT estimate</td>
</tr>
<tr>
<td></td>
<td>Observational estimate</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; RCT, randomised controlled trial

1. For women aged 50–59 years
2. For full source references, see the full guideline

**Type 2 diabetes**

1.4.8 Explain to women that taking HRT (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes.
1.4.9 Ensure that women with type 2 diabetes and all healthcare professionals involved in their care are aware that HRT is not associated with an adverse effect on blood glucose control.

1.4.10 Consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.

Breast cancer

1.4.11 Ensure that menopausal women and healthcare professionals involved in their care understand that HRT does not affect the risk of dying from breast cancer.

1.4.12 Using table 3, explain to women around the age of natural menopause that:

- the baseline risk of breast cancer for women around menopausal age in the UK varies from one woman to another
- HRT with oestrone alone is associated with little or no increase in the risk of breast cancer
- HRT with oestrone and progestogen can be associated with an increase in the risk of breast cancer
- any increase in risk of breast cancer is related to treatment duration and reduces after stopping HRT.
Table 3 Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different duration of HRT use and time since stopping HRT for menopausal women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Past users</th>
<th>Current users</th>
<th>Treatment duration &lt;5 years</th>
<th>Treatment duration 5–10 years</th>
<th>&gt;5 years since stopping treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women on oestrogen alone</td>
<td>RCT estimate</td>
<td>–</td>
<td>3 fewer (from 6 fewer to 1 more)</td>
<td>–</td>
<td>2 fewer (from 5 fewer to 1 more)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>0 fewer (from 2 fewer to 3 more)</td>
<td>2 more (from 0 to 5 more)</td>
<td>4 more (from 0 to 5 more)</td>
<td>2 more (from 1 fewer to 6 more)</td>
<td>2 fewer (from 4 fewer to 0)</td>
</tr>
<tr>
<td>Women on oestrogen plus progestogen</td>
<td>RCT estimate</td>
<td>–</td>
<td>2 more (from 2 fewer to 8 more)</td>
<td>–</td>
<td>3 more (from 0 to 7 more)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>1 fewer (from 5 fewer to 5 more)</td>
<td>7 more (from 6 more to 8 more)</td>
<td>5 more (from 2 more to 8 more)</td>
<td>9 more (from 4 more to 16 more)</td>
<td>4 fewer (from 7 fewer to 6 more)</td>
</tr>
<tr>
<td>Women on any HRT</td>
<td>RCT estimate</td>
<td>–</td>
<td>4 fewer (from 7 fewer to 3 more)</td>
<td>–</td>
<td>1 fewer (from 5 fewer to 6 more)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>0 fewer (from 0 fewer to 1 more)</td>
<td>7 more (from 5 more to 10 more)</td>
<td>5 more (from 1 more to 9 more)</td>
<td>10 more (from 3 more to 19 more)</td>
<td>0 fewer (from 1 fewer to 2 more)</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; RCT, randomised controlled trial

1 For women aged 50–59 years

For full source references, see the full guideline

Osteoporosis

1.4.13 Give women advice on bone health and discuss these issues at review appointments (see the NICE guideline on osteoporosis: assessing the risk of fragility fracture).
1.4.14 Using table 4, explain to women that the baseline risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another.

1.4.15 Using table 4, explain to women that their risk of fragility fracture is decreased while taking HRT and that this benefit:

- is maintained during treatment but decreases once treatment stops
- may continue for longer in women who take HRT for longer.

### Table 4 Absolute rates of any fragility fracture for HRT compared with no HRT (or placebo), different duration of HRT use and time since stopping HRT for menopausal women

<table>
<thead>
<tr>
<th>Women on any HRT</th>
<th>Difference in any fragility fracture incidence per 1000 menopausal women (see footnotes for information on baseline risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past users</td>
</tr>
<tr>
<td>Women on any HRT</td>
<td>RCT estimate(^1)</td>
</tr>
<tr>
<td>Observational estimate</td>
<td>140 fewer (from 28 fewer to 218 fewer)(^4)</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; RCT, randomised controlled trial

\(^1\) For women aged 50–59 years

\(^2\) Baseline risk = 69 per 1000 women (follow-up: 3.43 years)

\(^3\) Baseline risk = 78 per 1000 women (follow-up: 3.71 years)

\(^4\) Baseline risk = 333 per 1000 women (follow-up: 7 to 24 years)

\(^5\) Baseline risk = 15.4 per 1000 women (follow-up: 2.8 years)

\(^6\) Baseline risk = 106 per 1000 women (follow-up: 5 years)

For full source references, see the full guideline.
### Dementia

1.4.16 Explain to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown.

### Loss of muscle mass and strength

1.4.17 Explain to women that:

- there is limited evidence suggesting that HRT may improve muscle mass and strength
- muscle mass and strength is maintained through, and is important for, activities of daily living.

### 1.5 Diagnosing and managing premature ovarian insufficiency

#### Diagnosing premature ovarian insufficiency

1.5.1 Take into account the woman’s clinical history (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency.

1.5.2 Diagnose premature ovarian insufficiency in women aged under 40 years based on:

- menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) and
- elevated FSH levels on 2 blood samples taken 4–6 weeks apart.

1.5.3 Do not diagnose premature ovarian insufficiency on the basis of a single blood test.

1.5.4 Do not routinely use anti-Müllerian hormone testing to diagnose premature ovarian insufficiency.
1.5.5 If there is doubt about the diagnosis of premature ovarian insufficiency, consider anti-Müllerian hormone testing after seeking specialist advice (see the NICE guideline on fertility).

Managing premature ovarian insufficiency

1.5.6 Offer sex steroid replacement with a choice of HRT or a combined oral contraceptive to women with premature ovarian insufficiency, unless contraindicated (for example, in women with hormone-sensitive cancer).

1.5.7 Explain to women with premature ovarian insufficiency:

- the importance of starting hormonal treatment either with HRT or a combined oral contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated).
- that HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
- that both HRT and combined oral contraceptives offer bone protection
- that they should not use HRT as a contraceptive.

1.5.8 Give women with premature ovarian insufficiency and contraindications to hormonal treatments advice on bone and cardiovascular health, and symptom management (see also section 1.3).

2 Implementation: getting started

This section will be completed in the final guideline using information provided by stakeholders during consultation.

To help us complete this section, please use the comments form to give us your views on these questions:

1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.
2. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)

3 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

3.1 Women with or at risk of breast cancer

What is the efficacy of different treatments for menopausal symptoms in women who have had treatment for, or are at risk of, breast cancer?

Why this is important

Women with a history of breast cancer are currently denied hormonal treatment for menopausal symptoms but the available alternatives are less effective. There is limited evidence from randomised controlled trials on the efficacy of treatments (specifically on vaginal oestrogen) for menopausal symptoms in women who have had treatment for, or are at risk of, breast cancer. There is an urgent need for evidence-based licensed alternatives to traditional HRT in women with breast cancer and other hormone-sensitive malignancies. Randomised controlled trials or large cohort studies are needed to understand the effects of HRT in women with or at risk of breast cancer, and to investigate if there is a difference in breast cancer recurrence, mortality and tumour aggression with different types of HRT.

3.2 Effects of HRT on breast cancer risk

What is the difference in the risk of breast cancer in menopausal women on HRT with either progesterone, progestogen or selective oestrogen receptor modulators?

Why this is important

Fear of breast cancer deters many women from taking HRT, even in the presence of debilitating menopausal symptoms. There is a lack of evidence from randomised controlled trials directly comparing the risk of breast cancer...
in menopausal women on HRT with either progesterone, progestogen or selective oestrogen receptor modulators. There is a need for a national registry of women with breast cancer.

Optimising the risk–benefit profile of HRT will potentially reduce morbidity and mortality from breast cancer in women who need HRT over the long term because of continuing menopausal symptoms.

3.3 **Effects of HRT on venous thromboembolism risk**

How does the preparation of HRT affect the risk of venous thromboembolism (VTE)?

**Why this is important**

An increase in the risk of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) is a significant side effect of HRT, particularly as PEs can be fatal. This risk appears to be greater with oral than transdermal HRT. DVT risk increases with age and BMI, among other risk factors.

The progestogen component of HRT may also influence the risk of a DVT, which may be greater with androgenic synthetic progestogens than natural progesterone (but findings from observational studies need confirmation).

Most women in the UK take oral HRT comprising oestrogen combined with a synthetic progestogen, and the use of progesterone is less common.

Randomised controlled trials are needed to compare oral with transdermal HRT, and HRT containing different types of progestogens. These trials should measure coagulation factors and the incidence of VTE in women at increased risk of VTE for whom transdermal oestrogen is indicated.

3.4 **Effects of HRT on dementia risk**

What are the effects of early HRT use on the risk of dementia?

**Why this is important**

Concern about the prospect of dementia in older age is increasing and any beneficial effect on the future risk of dementia will be important to women who are considering using HRT. There is a need for good-quality observational
studies on how early HRT use affects dementia risk in women with early
natural menopause, including women with premature ovarian insufficiency.

3.5 Premature ovarian insufficiency

What are the main clinical manifestations of premature ovarian insufficiency
and the short- and long-term impact of the most common therapeutic
interventions?

Why this is important

Women with premature ovarian insufficiency can experience the effects of
menopause for most of their adult life. This can lead to reduced quality of life
and an increased risk of osteoporosis, cardiovascular disease and probably
also dementia. There is uncertainty about the diagnosis, time course and
management of premature ovarian insufficiency. For example, it is possible
that different interventions produce different outcomes in terms of quality of
life, and bone, cardiovascular and brain protection. Combined oral
contraceptives are often prescribed when this might not be the best treatment
in terms of quality of life and preservation of bone density and cardiovascular
health. Short- and long-term outcomes of HRT versus combined oral
contraceptives in women with premature ovarian insufficiency therefore need
to be investigated.

Development of a collaborative premature ovarian insufficiency registry would
allow the collection of high-quality demographic, biobank (genomic) and
clinical data in order to clarify:

- the diagnosis and presentation of premature ovarian insufficiency
- the impact of therapeutic interventions such as combined oral
  contraceptives, HRT and androgens
- the long-term impact of premature ovarian insufficiency on bone density
  and fracture, and cardiovascular and cognitive health.
4 Other information

4.1 Scope and how this guideline was developed

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Women’s and Children’s Health to develop this guideline. The Centre established a Guideline Development Group (see section 5), which reviewed the evidence and developed the recommendations.

The methods and processes for developing NICE guidelines are described on the NICE website.

4.2 Related NICE guidance

Details are correct at the time of consultation on the guideline (June 2015). Further information is available on the NICE website.

General

- Patient experience in adult NHS services (2012) NICE guideline CG138
- Medicines adherence (2009) NICE guideline CG76

Condition-specific

- Lipid modification (update) (2014) NICE guideline CG181
- Urinary incontinence (2013) NICE guideline CG171
- Familial breast cancer (2013) NICE guideline CG164
- Fertility (2013) NICE guideline CG156
- Osteoporosis (2012) NICE guideline CG146
- Epilepsy (2012) NICE guideline CG137
1. **Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)** (2012) NICE technology appraisal guidance 161

2. **Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)** (2011) NICE technology appraisal guidance 160

3. **Chronic heart failure** (2010) NICE guideline CG108

4. **Denosumab for the prevention of osteoporotic fractures in postmenopausal women** (2010) NICE technology appraisal guidance 204

5. **Depression in adults** (2009) NICE guideline CG90


7. **Early and locally advanced breast cancer** (2009) NICE guideline CG80

8. **Heavy menstrual bleeding** (2007) NICE guideline CG44

5 The Guideline Development Group, National Collaborating Centre and NICE project team, and declarations of interests

5.1 Guideline Development Group

Terry Aspray
Consultant Physician, Musculoskeletal Unit, Freeman Hospital

Claire Bowring
Lay member

Melanie Davies (until November 2014)
Consultant Obstetrician and Gynaecologist, University College London Hospitals

Deborah Holloway
Nurse Consultant Gynaecology, Guys and St Thomas’s NHS Foundation Trust

Sally Hope
GP, Oxford, Oxfordshire

Deborah Keatley
Lay member

Mary Ann Lumsden
Professor of Medical Education and Gynaecology (Reproductive and Maternal Medicine) and Head of University of Glasgow Campus, Glasgow Royal Infirmary

Sara Moger
Lay member

Prunella Neale
Practice Nurse, Herschel Medical Centre, Slough
Nicholas Panay
Consultant Gynaecologist and Specialist in Reproductive Medicine, Queen Charlotte’s and Chelsea Hospital and Chelsea and Westminster Hospital, London

Anthony Parsons
Consultant Community Gynaecologist, Coventry and Warwickshire Partnership Trust

Imogen Shaw
GP, Finchingfield, Essex

Christine West (from January 2015)
Consultant Gynaecologist, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh

Expert Advisers

Charlotte Coles
Consultant Clinical Oncologist, Addenbrooke’s Hospital, Cambridge

Peter Collins
Professor of Clinical Cardiology, Imperial College London

Rebecca Hardy
Programme Leader for Medical Research Council Unit for Lifelong Health and Aging, University College London

Adrian Harnett
Consultant Clinical Oncologist, Norfolk and Norwich University Hospital

Myra Hunter
Professional Lead for Clinical Health Psychology, South London and Maudsley Foundation Trust
5.2 National Collaborating Centre for Women’s and Children’s Health

Grammati Sarri
Senior Research Fellow and Guideline Lead (from October 2014)

Melanie Davies
Clinical Director (from December 2014)

Annabel Flint
Project Manager (from June 2014)

Yelan Guo
Research Fellow (from March 2014)

Sadia Janjua
Research Fellow (from July 2014)

Amy Wang
Research Fellow (from June 2014)

Hugo Pedder
Statistician (from September 2014)

Paul Jacklin
Senior Health Economist (from January 2015)

Omnia Abdulrazeg
Research Fellow (September to December 2014)

Zosia Backles
Information Scientist (from November 2014)

Rosalind Lai
Information Scientist (until October 2014)

David James
Clinical Director (until November 2014)
5.3 \textbf{NICE project team}

Sharon Summers-Ma
Guideline Lead
5.4 Declarations of interests

The following members of the Guideline Development Group made declarations of interests. All other members of the Committee stated that they had no interests to declare. The conflicts of interest policy (2007) was followed until September 2014, when an updated policy was published.
<table>
<thead>
<tr>
<th>Member</th>
<th>Interest declared</th>
<th>Type of interest</th>
<th>Decision taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terry Aspray</td>
<td>Membership of Advisory Board for Lilly Pharmaceuticals</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Terry Aspray</td>
<td>Paid presentation to Sexual and Reproductive Health North East</td>
<td>Non-personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Terry Aspray</td>
<td>Lecture on Vitamin D in surgery</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Claire Bowring</td>
<td>Chair of the National Osteoporosis Society and member of the NICE osteoporosis Guideline Development Group</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Private medical practice based at the Centre for Reproductive and Genetic Health; occasional patients seen at London Medical</td>
<td>Non-specific personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Educational grants received for lectures</td>
<td>Non-specific non-personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Clinical adviser to Medicines and Healthcare products Regulatory Agency (MHRA)</td>
<td>Non-specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Member of European Society for Human Reproduction and Embryology (ESHRE) Member of British Menopause Society</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Medical Adviser, Turner Syndrome Support Society</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Co-Chair, Guideline Development Group on Premature Ovarian Insufficiency, ESHRE</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Invited speaker presenting draft Premature Ovarian Insufficiency guideline ESHRE meeting</td>
<td>Specific non-personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Registration/accommodation for attendance at International Menopause Society (IMS) meeting (Novo Nordisk)</td>
<td>Specific non-personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Direct payment for medicolegal advice</td>
<td>Non-specific personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Speaker European Paediatric &amp; Adolescent Gynaecology conference</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Speaker patient support group Turner syndrome</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Name</td>
<td>Description</td>
<td>Type of Financial Interest</td>
<td>Declaration of Interests</td>
</tr>
<tr>
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</tr>
<tr>
<td>Melanie Davies</td>
<td>Co-author abstract &amp; oral presentation British Menopause Society ‘Comparison of efficacy of oral contraceptive pill and hormone replacement therapy for young women with premature ovarian insufficiency’ V Talaulikar, E Yasmin, M Davies, G Conway</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Melanie Davies</td>
<td>Co-author abstract accepted Royal College of Obstetricians and Gynaecologists (RCOG) international congress, Brisbane: treatment for premature ovarian insufficiency</td>
<td>Specific personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Holloway</td>
<td>Chaired a Royal College of Nursing (RCN) women’s health conference sponsored by Bayer. Fee was paid directly to the RCN</td>
<td>Non-personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Sits on the women’s health board at the MHRA</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Deputy editor of ‘Maturitas’</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Received a lecture fee from Consilient Health to give a workshop to drug representatives on third generation oral contraceptive pills and thromboembolic risk following a European medicines statement</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Received a lecture fee for presentations at two GP conferences speaking on male osteoporosis</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Attended a GP Round Table Forum on HRT with a write up in ‘GP magazine’</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Received lecture fees for non-promotional educational lectures for GPs</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Gave a symposium talk on Vitamin D3 at the National Osteoporosis Conference, Birmingham</td>
<td>Non-specific personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Lectured to the Oxfordshire Deanery GP registrar year on osteoporosis. Educational fee paid by Oxfordshire GP Deanery</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Sally Hope</td>
<td>Regular contributor to ‘Menopause Matters’ magazine. Small payment made by subscription of members of the</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Name</td>
<td>Role</td>
<td>Relationship</td>
<td>Financial Declaration</td>
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</tr>
<tr>
<td>Deborah Keatley</td>
<td>Public member of National Cancer Research Institute Brain Tumour Clinical Studies Group and member Palliative Care subgroup</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Keatley</td>
<td>Public member of National Institute of Health Research Health Technology Assessment Emergency and Elective Specialist Care TIDE Panel</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Keatley</td>
<td>Member of NI Cancer Research Consumer Forum</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Keatley</td>
<td>Member of NI Public Health Research Network</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Keatley</td>
<td>Education level 6 course</td>
<td>Personal specific non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Deborah Keatley</td>
<td>Presentation on peri-menopause</td>
<td>Personal specific non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Sits on the women's health board at the MHRA and has recently been appointed as the chair of the National Collaborating Centre for Women's and Children's Health consortium board</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Elected president for the International Menopause Society but will not become president until after the guideline is scheduled to be published</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Presentation: 'The place of guidelines in the management of menopausal women', Post Reproductive Health Meeting, London</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Presentation: 'towards better health for women in mid-life and beyond', The Paul Stya Oration, Delhi.</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Presentation: 'The role of guidelines in evidence based health care', FIGO/Sri Lankan College of O&amp;G Meeting in Sri Lanka</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Presentation: 'Clinical guidance in the care of menopausal women', Panel discussion at US Endocrine Society Meeting</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mary Ann Lumsden</td>
<td>Presentation: 'Managing the menopause in young and not so</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Name</td>
<td>Details</td>
<td>Financial Declaration</td>
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</tr>
<tr>
<td>Sara Moger</td>
<td>Chief executive of the British Menopause Society</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Prunella Neale</td>
<td>Applied for sponsorship to Abbott Pharmaceuticals to cover the delegate fee to attend 1 day of the British Menopause Conference, June 2015</td>
<td>Non-specific personal financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Sat on an advisory board for Pfizer and attended sponsored conferences. Chaired sessions on OCP and vaginal dryness sponsored by Bayer and Novo-Nordisk</td>
<td>Personal pecuniary</td>
<td>Declare</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Attended advisory board meeting coordinated by Shinogi pharmaceuticals looking at developing a vulvo-vaginal questionnaire</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Principal investigator – premature ovarian insufficiency (POI) registry 2013 onwards</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Chair Post Reproductive Clinical Study Group – RCOG research committee 2010 onwards</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Chaired 1 session and lectured at IMS meeting: Bayer: Chair – Mirena in peri- and post-menopause Besins: Lecture – Role of body identical hormone therapy</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Event Type</td>
<td>Personal pecuniary</td>
<td>Participate</td>
</tr>
<tr>
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</tr>
<tr>
<td>Novo Nordisk: Lecture – ultra low dose hormone therapy</td>
<td>Ongoing menopause advisory work and lecturing for Shionogi, Abbott and Pfizer pharmaceuticals</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: International Society of Gynaecological Endocrinology Meeting (ISGE)</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
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<tr>
<td>Nick Panay</td>
<td>Premature ovarian insufficiency lecture</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Androgen lecture</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
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<tr>
<td>Nick Panay</td>
<td>Bio-identical hormone lecture</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: Menopause: natural selection or modern disease RSM presidential address</td>
<td>Personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: premature ovarian insufficiency: women’s health concern RCOG</td>
<td>Personal non-financial</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: Premature ovarian insufficiency: Irish Menopause Society meeting</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: HRT: clarity at last: Annual Professional Development meeting RCOG</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
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<tr>
<td>Nick Panay</td>
<td>Presentation: Premature ovarian insufficiency: post-reproductive health meeting RCOG</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: Conference organiser post-reproductive health meeting RCOG</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: Premature ovarian insufficiency: Abbott Health professional meeting RCOG</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nick Panay</td>
<td>Presentation: Postmenopausal health meeting: Imperial Staff Postgraduate Forum</td>
<td>Personal non-pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Name</td>
<td>Publication</td>
<td>Specific personal financial</td>
<td>Declare and participate</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Anthony Parsons</td>
<td>Attended IMS meeting – attendance fee paid by Novo Nordisk</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Anthony Parsons</td>
<td>Honorarium received from Novo Nordisk for attendance at advisory board meeting. Agenda included items relevant to the guideline but AP did not take part in these discussions</td>
<td>Personal pecuniary</td>
<td>Declare and participate</td>
</tr>
</tbody>
</table>