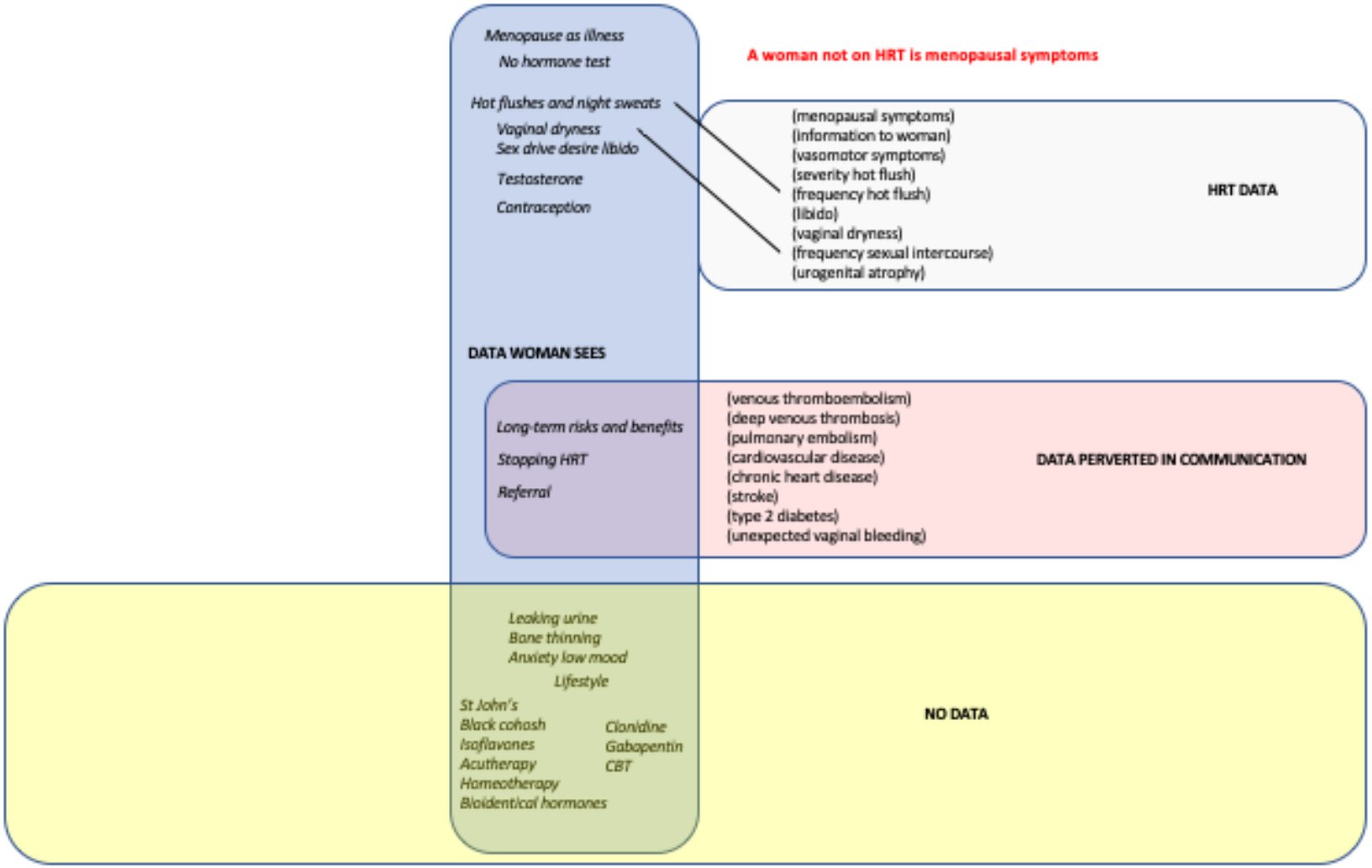
Study 3

(woman) = (premature menopause) ± (oral contraception) ± (hormone replacement therapy)

A UK health system creature

DATA WOMAN SEES	DATA UNKNOWN USER SEES	DATA HEALTHCARE PROFESSIONAL SEES
Menopause as illness	$[woman] = [(premature\ menopause) \pm (oral\ contraception) \pm (HRT)]$	$(premature\ menopause) \in (menopausal\ symptoms)$
Hot flushes and night sweats	$(premature\ menopause) = [(age \geq 40) \pm (uterus) + (menopausal\ symptoms) + (2\ FSH\ samples)]$	$(diagnosis) = (information\ to\ woman)$
Vaginal dryness *Sex drive desire libido*	$(menopausal\ symptoms) = (woman) - (HRT)$	
	$HRT = [(age \geq 40) \pm (menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)]$	$(vaginal\ dryness) = (urogenital\ atrophy)$
	$(woman's\ baseline\ characteristics) \notin (menopausal\ symptoms)$	
	$HRT = (systemic\ HRT) + (local\ topical\ hormone\ application)$	
Leaking urine *Bone thinning* *Anxiety low mood*	$(menopausal\ symptom_f) \subset \{urogenital\ atrophy\}$ $(menopausal\ symptom_b) \subset \{urinary\ incontinence\}$	
No hormone test	$(menopausal\ symptom_{bo}) \subset \{osteoporosis\}$	
Lifestyle		$(oral\ contraception) = (no\ hormonal\ investigation)$
St John's *Black cohosh* *Isoflavones* *Acutherapy* *Homeotherapy* *Bioidentical hormones*	$(lifestyle\ changes) \notin (HRT)$ $(obesity) \subset \{lifestyle\ changes\}$ $(alternative\ therapies) \notin (HRT)$	$(breast\ cancer) = (no\ St\ John's\ wort)$ $[risk\ of\ black\ cohosh\ and\ isoflavones]$ $> [benefit\ of\ black\ cohosh\ and\ isoflavones]$
Clonidine *Gabapentin* *CBT*		
Testosterone	$[(high\ risk\ of\ VTE\ with\ HRT) + (low\ risk\ of\ DVT\ and\ PE)] > [risk\ with\ oral\ HRT] > [risk\ with\ transdermal\ HRT]$	$(low\ libido) = (HRT) + (testosterone)$
Long-term risks and benefits	$[absolute\ risk\ of\ CVD\ with\ HRT] > [relative\ risk\ of\ CVD\ with\ HRT] \geq [risk\ of\ stroke\ with\ HRT]$ $> [(risk\ of\ CVD\ with\ oral\ HRT) > [risk\ of\ CVD\ with\ transdermal\ HRT]]$	$[risk\ of\ stroke\ with\ oral\ HRT] \geq [risk\ of\ stroke]$
	$(HRT\ withdrawal) = (increased\ risk\ of\ T2DM)$	$[risk\ of\ CHD\ with\ (HRT_{estrogen} + HRT_{progesterone})] \geq [risk\ of\ CHD\ without\ HRT]$
	$[risk\ of\ HRT_{related} breast\ cancer] < [cost\ of\ HRT_{related} breast\ cancer]$	$[risk\ of\ CHD\ without\ HRT] \geq [risk\ of\ CHD\ with\ HRT_{estrogen}]$
		$(risk\ of\ stroke\ age < 60 \in (negligible)$
	$[(HRT) - (exercise)] = (loss\ of\ muscle\ mass)$	$[high\ risk\ of\ VTE\ with\ HRT] > [oral\ HRT_{related} risks] > [transdermal\ HRT_{related} risks]$
Contraception		$(HRT) \pm (oral\ contraception) = (decreased\ risk\ of\ osteoporosis\ and\ CVD)$
Stopping HRT		$(withdrawal\ of\ HRT) = (menopausal\ symptoms)$
Referral		$(unexpected\ vaginal\ bleeding) \subset (endometrial\ cancer)$


Menopause as illness
No hormone test
Hot flushes and night sweats
Vaginal dryness
Sex drive desire libido
Testosterone
Contraception
A woman not on HRT is menopausal symptoms
(menopausal symptoms)
(information to woman)
(vasomotor symptoms)
(severity hot flush)
(frequency hot flush)
(libido)
(vaginal dryness)
(frequency sexual intercourse)
(urogenital atrophy)
HRT DATA
DATA WOMAN SEES
Long-term risks and benefits
Stopping HRT
Referral
(venous thromboembolism)
(deep venous thrombosis)
(pulmonary embolism)
(cardiovascular disease)
(chronic heart disease)
(stroke)
(type 2 diabetes)
(unexpected vaginal bleeding)
DATA PERVERTED IN COMMUNICATION
Leaking urine
Bone thinning
Anxiety low mood
Lifestyle
St John's
Black cohash
Isoflavones
Acutherapy
Homeotherapy
Bioidentical hormones
Clonidine
Gabapentin
CBT
NO DATA

1. Data analysis[1]

MENOPAUSE		
WHAT THE WOMAN SEES ON WEBSITES	**EVIDENCE UNDERPINNING IN FULL NICE GUIDELINE**	**NICE CLINICAL GUIDELINE**
Royal College of Obstetricians & Gynaecologists (UK) National Institute for Health Care Excellence (UK)		
(RCOG HRT 2022a and c) and other websites	(NICE HRT 2015)	(NICE NG23 2015)
DATA is *what the woman sees in the order in which she sees it*	DATA is *clinical trials whether deemed randomized or not, cohort studies, developers' experience,* and *methods, evidence, and recommendations*	DATA is *clinical guideline.*
USER is *nonprofessional woman*	USER is *unknown*	USER is *healthcare professional*

Results page 56.

[1] In Study 1 page 87, it was shown that experience is absent from evidence based medicine. This is hurtful to women and society (Goldenberg 2006).

2. Hormone therapy for menopausal symptoms

2.1. RCOG website *Home → For the public → Menopause and later life → HRT and alternatives*

RCOG website "…HRT and alternatives…" provides "…Information for women, their partners and families about hormone replacement therapy (HRT) and the alternatives for treatment of menopausal symptoms…" (RCOG HRT 2022a), click here for the website, and see the following pages.

2.1.1. Immediately after defining the user, this 'guideline for the public' states: 'What is HRT?'. 'Alternatives' come lumped together later below.

2.1.2. It is explained that menopause is associated with reduced production of estrogen which leads to menopausal symptoms. After listing the symptoms, it is explained that HRT is a form of 'topping up' age related hormonal changes.

2.1.3. The first and second symptoms of menopause listed are hot flushes and night sweating. This is important because, the implication is that HRT treats hot flushes as well as other symptoms of menopause. That this is false is clear from: (i) information given to the public by RCOG through the link RCOG provided on that page and discussed below; (ii) information given to the public by NHS through the link provided by RCOG on that page and discussed below; (iii) information given by NICE to health professionals through the link provided by RCOG on that page and discussed below; and (iv) information given to the public including health professionals by Women's Health Concern in two links provided by RCOG on that page, and discussed below.

2.1.4. The third symptom of menopause for treatment by HRT is vaginal dryness. Note that HRT is systemic and not locally administered. In other words, hormone containing vaginal crème or lubricants, are not under consideration.

2.1.5. 'Loss of sex drive' is a symptom of menopause according to (RCOG HRT 2022a).[2]

2.1.6. Stress incontinence is the fifth symptom of menopause to be treated by HRT.

2.1.7. The last symptom of menopause to be treated by HRT is 'bone thinning' which 'leads to osteoporosis and fractures'. However, osteoporosis is an radiological finding and no investigations whatsoever are recommended for the healthy ageing woman.

[2] In (RCOG HRT 2022b) website, that symptom is "…Loss of interest in sex…". However, in addition to the symptoms listed in 2.1.3 to 2.1.7, the menaopausal woman may also expect 'dizziness, mood swings, memory problems, and weight gain'. In (NHS HRT 2022a) website, the symptom under discussion is "…reduced sex drive…".

HRT and alternatives

Information for women, their partners and families about hormone replacement therapy (HRT) and the alternatives for treatment of menopausal symptoms

What is HRT?

Hormone replacement therapy, or HRT, is widely used to treat menopausal symptoms.

As you approach the menopause, your ovaries produce less and less of the hormone estrogen. Estrogen controls a woman's reproductive cycle as well as controlling other functions, including bone density, skin temperature and keeping the vagina moist. This reduction in estrogen causes most symptoms associated with the menopause, including:

- Hot flushes
- Night sweats
- Vaginal dryness
- Loss of sex drive
- Stress incontinence (leaking urine when you cough or sneeze)
- Bone thinning (which can lead to osteoporosis and fractures)

The aim of HRT, as its name suggests, is to replace or 'top up' the body's natural supply of estrogen. Estrogen also stimulates the lining of the womb, so you will also need to take another hormone, progestogen, at the same time to protect your womb lining.

If you have had a hysterectomy, you may not need progestogen and may be prescribed estrogen-only HRT. However, depending on the reason for your hysterectomy and the type of hysterectomy you have had, you may be advised to use estrogen and progestogen combined HRT.

You can read about various treatment options for symptoms of the menopause, including lifestyle changes, prescribed and non-prescribed treatments, in the RCOG patient information Treatment for symptoms of the menopause.

Find out more about HRT

The following links provide information and advice about HRT:

- HRT - general overview (NHS)
  Overview of HRT, including different types, the benefits and the risks
- HRT - clinical guideline (NICE)
  Evidence-based national guideline on menopause, including information about HRT
- HRT factsheet (Women's Health Concern)
  General overview of HRT
- Benefits and risks of HRT (Women's Health Concern)
  Facts about the safety and suitability of HRT

Alternatives to HRT

Why would I choose an alternative to HRT?

Not every woman chooses HRT or can have HRT to help their symptoms of the menopause. For you, this may be because:

- You want an alternative treatment that works especially well for one particular symptom
- You have concerns about the safety and side effects of HRT
- You would prefer alternative treatments to help alleviate symptoms of the menopause

What are the alternatives to HRT?

The alternatives to HRT can be broadly classified as:

- **Herbal medicine** - a practice based on the use of plants or plant extracts to relieve symptoms, e.g. evening primrose oil or St John's Wort
- **Alternative medicine** - a range of therapies used instead of conventional medicine, such as acupressure, acupuncture and homeopathy
- **Complementary therapy** - interventions that tend to be used alongside conventional medicine, e.g. aromatherapy with HRT
- **Non-hormonal medical treatments** - treatments prescribed by your doctor, such as antidepressants

Find out more about alternatives to HRT

The following links provide information about the alternatives to HRT:

- Treatment for symptoms of the menopause (RCOG)
  Overview of treatment options for symptoms of the menopause
- Complementary/alternative therapies for menopausal women (Women's Health Concern)
  Overview of HRT alternatives and complimentary therapies

Making a choice about your treatment

There will be choices to make about the type of treatment you wish to receive. You will probably have a lot of questions and may wish to discuss your options with family and friends. To begin with, try to get answers to three key questions:

- What are my options?
- What are the pros and cons of each option for me?
- How do I get support to help me make a decision that is right for me?

For more information about working with your healthcare professional to make the right choice for you, please visit the NHS Shared Decision Making website.

About the links on this page

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Medical terms explained

A–Z of common medical words in women's health

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Mood changes and depression

Next page - Sex and relationships after the menopause

Sex and relationships after the menopause

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2.2. RCOG website *Home → For the public → Browse all patient information leaflets → Treatment for symptoms of the menopause*

Under RCOG website "…Treatment for symptoms of the menopause…" (RCOG HRT 2022c) or click here.

2.2.1. In addition to the symptoms of menopause listed on the RCOG webpage discussed in section 2.1., the menopausal woman may expect 'low mood/feeling anxious, joint and muscle pain', as well as 'loss of interest in sex' – with or without (complete) loss of sex drive is not mentioned.

2.2.2. After introducing menopause, the user is informed that hormone tests (clinical investigations) are not required prior to HRT. Suffice to comment at present that HRT is an individualized treatment. It may suffice to comment and also to emphasize that HRT is an individualized treatment within RCOG and NICE data discussed below.

2.2.3. Options for treatment are in order of appearance: (i) lifestyle changes; (ii) Traditional Herbal Registration number labelled St John's wort, black cohosh, and isoflavones are suggested and interactions with other medications is cautioned; (iii) acutherapy and homeotherapy may benefit and more research needed; (iv) aromatherapy; (v) bioidentical hormones; (vii) HRT; (viii) clonidine or gabapentin; (ix) cognitive behavioural therapy or CBT.

2.2.4. HRT is introduced as a replacement for age related decreased estrogen production. In addition, progestogen and testosterone may also need to be replaced. If interested, discussion with healthcare professional should include short terms and longer term benefits and risks.

2.2.5. Various types of HRT are briefly discussed based on the presence or absence of a uterus and vaginal bleeding depending on the type of HRT. Finally "…Women who notice a low sex drive after the menopause may be offered another hormone called testosterone. This is a hormone linked to sex drive in both men and women…" and "…HRT is available as oral tablets, skin patches, injections, body gel or spray, or vaginal ring, cream or pessary…".

2.2.6. HRT is stated to be effective and safe, worldwide.

2.2.7. The benefits of HRT are for hot flushes, improved mood, sexual desire, vaginal dryness, and keeping bones strong.

2.2.8. The risks of HRT are: (i) no risk of breast cancer on estrogen only; (ii) some risk of breast cancer which increases with time and decreases with cessation of HRT on estrogen and progestogen; (iii) an individual risk for breast cancer associated with smoking and drinking; (iv) increased risk of blood clotting and stroke.

2.2.9. A woman suffering symptoms of menopause and who had previously suffered breast cancer or an embolic episode is reassured that HRT may be an option.

2.2.10. A woman suffering diabetes and/or hypertension and also suffering from symptoms of menopause is reassured that HRT may be an option.

2.2.11. A role for HRT in the development or prevention of dementia is stated to be unknown.

2.2.12. Contraception in addition to HRT is recommended for 1 – 2 years depending on when HRT is initiated.

2.2.13. There are no set limits to how long HRT can be taken. However, "…You can stop your HRT suddenly or reduce gradually before stopping it. *The chances of your symptoms coming back is the same either way*…" emphasis added, (RCOG HRT 2022c).

2.2.14. Menopause specialist introduced, CBT for low mood, testosterone for lost sex drive, and vaginal crème for dryness.

2.2.15. Some points on premature menopause. Finally, shared decision making.

2.3. What does the woman see about HRT, and how this relates to: (i) what was seen by RCOG and NICE developers (NICE HRT 2015); and (ii) what the health professional sees or the HRT guideline (NICE NG23 2015), in order of their appearance to the woman:[3]

Menopause as illness

2.3.1. The first thing the woman see, whether logged onto or RCOG webpage on 'treatment for menopause' (RCOG HRT 2022a) or 'HRT' (RCOG HRT 2022a), is a confabulation of menopause and its symptoms. Menopause is explained as age related decline in estrogen levels. HRT is explained as a 'topping up' of those hormones which may have decreased due to ageing. In other words, that *symptoms of (physiological, age related) menopause require HRT*. That this is an unsophisticated view of menopause is (self-)evident in information given by RCOG and NICE in (NICE NG23 2015): HRT is treatment for premature menopause and the same time no evidence on premature menopause is considered, discussed below.

2.3.2. Evidence supporting 'diagnosis of menopause' as a condition requiring treatment is in (NICE HRT 2015) is:

[3] The user of (RCOG HRT 2022a) and (RCOG HRT 2022c) is the nonprofessional woman. The user of (NICE NG23 2015) is the healthcare professional: "…The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual…" (NICE NG23 2015) page 2. The user of (NICE HRT 2015), which is the evidence and methods on which (NICE NG23 2015) was based, was not specificed in that product.

under "…Diagnosis of perimenopause and menopause…

…a review of twenty-one studies (mostly graded moderate to low quality by NICE) concluded that "…Being aged less than 55 or 60 years may reduce the chances of being perimenopausal but being over 55 did not increase the chance of being perimenopausal (very low quality evidence). No other age groups (less than 45 years or less than 50 years) were useful to distinguish perimenopausal from postmenopausal women…The presence of [vasomotor symptoms] alone was not useful to distinguish perimenopausal from postmenopausal women (moderate to very low quality evidence)…No endocrine tests (inhibin A or inhibin B) were found useful to distinguish perimenopausal from postmenopausal women (moderate quality evidence)…" (NICE HRT 2015), pages 59-60. In other words 'diagnosis' of menopause is by age and unrelated to any measurable changes in estradiol levels (NICE HRT 2015) page 17. This is confirmed also in (NICE HRT 2015) page 62 where it is specifically recommended not to measure estradiol among other investigations.

under "…Classification systems for the diagnosis of menopause…

…The aim of this review was to identify whether the use of structured classification systems are useful tools to assess different stages of the menopause by guiding further investigation and treatment for menopausal symptoms, beyond using a clinical history alone…No clinical evidence was found for this review question…" (NICE HRT 2015), pages 63-64

HRT = [(menopausal symptoms in woman age ≥ 40) ± (uterus)] ± (oral contraception)

2.3.3. In fact, estrogen levels by age in healthy women are poorly reported so as to be effectively unknown.[4] An absolute *decline* in free and bound

[4] (Stanczyk and Clarke 2014) suggest estradiol levels are <20 pg/ml for both prepubertal children and postmenopausal women which is to say that the physiological indicator is meaningless as measured and reported; the authors discuss challenges in measuring and standardizing estradiol measurements. In 374 postmenopausal women, serum estradiol ranged from 1.0 to 45.2 pg/mol depending on assay method (Lee et al. 2006). (Conklin and Knezevic 2020) give <30 pg/ml for postmenopausal women without reference (no citation) and 30-60 pg/ml for postmenopausal women on HRT also without reference; in other words hormonal status of some menopausal women before and after HRT remains unchanged in addition to being simply 'less than 30 or 60 pg/ml' in all menopausal women; these authors also recommend mass spectrometry to complement estradiol clinical investigations. For humans in general, (Soldin and Soldin 2009) give estradiol levels 25.4 - 229.0 pg/ml measured by immunoassay and 109 - 630 pg/ml measured by mass spectrometry. Mass spectrometry is essential to estimate comparatively low concentrations of testosterone in sera of children and women and immunoassays are unreliable for such purpose (Taieb et al. 2003). Menopause serum estradiol level is tightly linked to diet and nutritional status, regardless of race and country of residence for example see (Goldin et al. 1986; Shimizu et al. 1990). (Wang et al.

testosterone in ageing men, *if present*, is dependent on diverse factors such as being *less* obese, *not* drinking alcohol, and when during the day the blood sample was taken.[5] To the best of my knowledge, there are no definitive measurements showing estrogen level dynamics in healthy ageing women which is obviously orders of magnitude more complex than testosterone dynamics in ageing men.

2.3.4. RCOG and NICE recommend HRT as a treatment for menopausal symptoms, and symptoms may resume with cessation of HRT. In fact, symptomatic treatment of a disease, for example antipyretics during a febrile viral illness, may alleviate patient suffering, and improve prognosis. However, menopause is in fact an conserved evolutionary mechanism which had conferred survival fitness on early non-*Homo sapiens*.[6] In general, the term 'palliative treatment' often refers to symptomatic treatment of a fatal condition.

2.3.5. In (NICE NG23 2015) page 5-6: "…Diagnosis of perimenopause and menopause…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 and are not using hormonal contraception; menopause based on symptoms in

2015) urge caution when interpreting menopausal serum estradiol level measured with immunoassays as those methods are pushed to limits of *sensitivity*, and outline how mass spectrometry may complement clinical sex hormone investigations, and advantages of the latter technique other than sensitivity such as preserving more of a sample in a biobank. See also (Wooding et al. 2015) for limits of postmenopausal serum estradiol *detection*. Further studies were recommended by (Handelsman et al. 2020): after measuring estradiol level changes using an ultrasensitive method, health benefits were found for postmenopausal females, males, children, and mice, see also (Kushnir et al. 2008). Some estradiol measurement and standardization technical challenges in industry outlined in (Thienpont and De Leenheer 1998). The ratio of estradiol to esterone as well as levels of other steroid hormones in 29 premenopausal women and 9 postmenopausal women is reported in (Rothman et al. 2011).

[5] To appreciate how 'testosterone changes in ageing men?' promptly leads to 'which man living roughly how around what time we exactly take sample?' see (S. M. Harman and Tsitouras 1980; Feldman et al. 2002; S. Mitchell Harman et al. 2001)

[6] See (Hawkes et al. 1998; Hill and Hurtado 1991). The 'grandmother hypothesis', in loose terms the 'mother effect' in evolutionary models, suggests postmenopausal women confer reproductive advantage on a postmenopausal woman's kin, and not only her grandchildren as communicated by (Melby and Lampl 2011); putative authors of the grandmother hypothesis are also misattributed by (Melby and Lampl 2011). Actions and knowledge (or culture) preserved by menopausal women confers selective advantage in ways not including warming up babies with hot flushes (Sievert and Masley 2015). (Chan, Gomes, and Singh 2020) suggest to 'de-evolve' menopause.

women without a uterus….Take into account that it can be difficult to diagnose menopause in women who are taking hormonal treatments, for example for the treatment of heavy periods…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…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.[7]…Consider using a FSH test to diagnose menopause only: 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 recommendations on diagnosing and managing premature ovarian insufficiency)…" (NICE NG23 2015) pages 5-6. In other words

HRT = [(age ≥ 40 + vasomotor symptoms) ± (uterus) ± (oral contraception)]

2.3.6. That menopause and not premature ovarian insufficiency is in fact an age related and conserved survival mechanism is discussed in paragraphs 2.3.3. and 2.3.4. of the present work and see also (Clausius 1857).

Hot flushes and night sweating or vasomotor symptoms

2.3.7. As mentioned above, the information that HRT treats hot flushes and night sweats is false because the same set of guidelines by RCOG and NICE also provide the information that hot flushes and night sweats may/will resume on cessation of HRT.

2.3.8. Lack of evidence to support HRT for menopausal vasomotor symptoms in (NICE HRT 2015):

under "…Diagnosis of perimenopause and menopause…

see paragraph 2.3.2.

under "…Managing short-term symptoms…

…What is the most clinical and cost-effective treatment for the relief of individual menopause- related symptoms for women at menopause?

…A total of 32 RCTs of 12 treatment classes (placebo, sham acupuncture, oestrogen plus progestogen non-oral, oestrogen plus progestogen oral, tibolone, raloxifene, SSRIs/SNRIs, isoflavones, Chinese herbal medicine, black cohosh, multibotanicals, acupuncture) were included for the NMA for

[7] This recommendation in this Guideline for health professionals is confusing and spurious: "…The challenge: stopping the use of folliclestimulating hormone tests to diagnose menopause in women aged over 45 years… If a woman is aged over 45 years and has not had a period for at least 12 months, or has vasomotor symptoms and irregular periods (or just symptoms if she doesn't have a uterus), this is adequate information to diagnose menopause and perimenopause respectively…" (NICE NG23 2015) page 21.

vasomotor symptoms (VMS) in women with a uterus. The quality of the evidence was low due to high heterogeneity although no inconsistency was identified in the network…

The main categories of interventions included in this review question were hormonal pharmaceutical treatments, non-hormonal pharmaceutical treatments, non-pharmaceutical treatments and psychological therapies. The main short-term menopausal symptoms that were the focus of this question were: frequency of [vasomotor symptoms or hot flushes and night sweats]; anxiety and low mood (excluding clinical depression) as aspects of psychological wellbeing; depression in the context of this review question referred to low mood, as no clinical diagnosis was made and this term (low mood) is used across the review; frequency of sexual intercourse as a measure of sexual function; joint and muscle aches and pains as indicators of musculoskeletal symptoms...

(anxiety low mood) = (anxiety low mood) – (depression)

(depression) = (low mood)

(low mood) = 0

In order to capture the spectrum of adverse events that may be associated with different treatments used for the relief of menopausal related symptoms, vaginal bleeding and discontinuation of treatment due to side-effects were selected as the most representative measures of women's experience of adverse events in the short term. Long-term adverse effects of HRT are covered in other sections (see Sections 10–10.8).

The presentation of evidence synthesis is divided into 2 parts, based on the type of analysis which was used to produce these syntheses: A network meta-analysis (NMA) was conducted for the outcomes of VMS, vaginal bleeding and discontinuation. These outcomes were prioritized because they are highly prevalent among women who are seeking treatment for menopausal symptoms and due to their importance on continuity of healthcare and further impact on women's experience of long-term outcomes. A totla[8] of 51 trials were included in the NMA for the outcomes of frequency of VMS, discontinuation and vaginal bleeding. Different number of trials contributed to each of NMA's networks (ranging from 4 to 32 trials for each network); Pair-wise meta-analyses were conducted for the outcomes of low mood, anxiety, frequency of sexual activities and frequency of joint and muscle aches and pains. A total of 69 trials were included in the pair-wise comparisons presenting these outcomes.

The NMA allows the synthesis of data from direct and indirect comparisons without breaking the randomisation of trials, in order to produce measures of class treatment effect and ranking of different interventions for the outcomes of interest. The NMA protocol was designed (please see full

[8] *sic*

details in Appendix D) with the aim to provide a methodologically and clinically appropriate basis to address this review question. In summary, stratified analysis was pre-selected based on the 3 main groups of women in menopause: women with and without a uterus and women with a history or at risk of breast cancer. For each of these strata, a list of the most appropriate interventions was organised; for example, for women with a uterus the combination of oestrogen plus progestogen was selected as the most appropriate hormonal treatment because progestogen is needed in women with a uterus to prevent the proliferation of the endometrium which could cause endometrial cancer if not controlled. Only non-hormonal treatments were included for the group of women with a history of breast cancer due to the potential risk of cancer recurrence. A class effect model was selected for the NMA with the underlying assumption that the effectiveness of different treatments under the same class would be comparable. This decision was made in order to maximise the availability of data and borrow strength from different trials. Non-hormonal treatments were common across the 3 strata. In addition, due to high variation in the way data was collected and presented in different trials in this area, we set up a clear and consistent approach of data collection. For example, we decided to examine the role of different treatments used to reduce the frequency rather than the severity of VMS. Assumptions were also made for the minimum duration of trials for inclusion in the NMA and the minimum acceptable criteria for mixed population studies. These assumptions are commonly made when a complex meta-analysis is designed and not only in the case of the NMA.

A number of studies (see full details in Appendix G) were excluded from further analysis due to not meeting the minimum acceptable criteria when studies used mixed populations (therefore the interpretation of results would be confounded by the effect of differences in women's baseline characteristics) and lack of information on the variation of estimate effects (no measures of standard error [SE] or standard deviation [SD] were presented). The majority of reasons for exclusion of studies would also apply in a conventional pair-wise meta-analysis in order to produce reliable estimates of effects of different interventions. For the small minority of studies excluded for purely statistical reasons, their results were discussed with the Guideline Development Group in relation to the interpretation of NMA results and whether the information of excluded studies would change the direction of their decision-making. This information was used as supplementary evidence to facilitate the group's discussion.

For full details see the review protocol in Appendix D…" (NICE HRT 2015) pages 75-76.

"…The network on frequency of VMS (32 RCTs of 9 treatment classes [placebo, sham acupuncture, raloxifene, SSRIs/SNRIs, isoflavones, Chinese herbal medicine, black cohosh, multibotanicals, acupuncture]) for women without a uterus did not include the hormonal treatment of oestrogen alone, as the relevant trials were excluded on the basis of either mixed population or lack of information on variation of effect estimates. Therefore, the final model included only non-hormonal and non-pharmaceutical treatments that

restricted the generalisation and applicability of its results, given that treatment of oestrogen alone is the current most common treatment offered to menopausal women without a uterus. Therefore the Guideline Development Group decided not to consider the results of this network for decision-making, given the limitation of their generalisability in the clinical context…" (NICE HRT 2015) page 95

(diagnosis) = (information to the patient)

"…A total of 51 studies were included in the NMA. There were 7 networks constructed for the 3 stratified groups of women in menopause (women with a uterus, women without a uterus and women with breast cancer). The quality of the NMA was assessed in terms of risk of bias of included trials, heterogeneity of results and inconsistency between direct and indirect evidence. All evidence contributed to the NMA was from randomised trials with a clear description of included population, which was women in menopause excluding those in premenopause. Data for some treatment comparisons included in the NMA were limited and most of the interventions were compared with placebo, and the Guideline Development Group recognised that this could bias the whole network. In addition, there was a wide variation in the way that studies assessed the outcome of VMS, for example reporting change values in scores, final values or summary measurements such as percentages. The focus of this review question for the NMA was on reporting the frequency of short-term symptoms with no inference made to the severity of these outcomes. That was a potential explanation of the increased heterogeneity observed in the networks given the wide variability of baseline characteristics of women in the trials, including the wide baseline variation on VMS….

…There is strong evidence that transdermal oestradiol plus progestogen greatly reduces the frequency of hot flushes in women with a uterus. Although there was no strong evidence of efficacy of oral oestrogen plus progestogen treatment, the health economic analysis and the Guideline Development Group's expert opinion supported its use in clinical practice…

"…Offer women HRT for vasomotor symptoms after discussing with them the short- term (up to 5 years) and longer-term benefits and risks. Offer a choice of preparations as follows: oestrogen and progestogen to women with a uterus; oestrogen alone to women without a uterus…" (NICE HRT 2015) pages 110-111.

In other words, there is no NICE evidence whatsoever to support NICE HRT treatment for menopausal vasomotor symptoms of hot flushes and night sweats.

(menopausal symptoms) = (frequency hot flush) + (anxiety low mood) + (frequency sexual intercourse) + (muscle pain)

(menopausal symptoms) = (woman) – (HRT)

(woman's baseline characteristics) $\notin$ (menopausal symptoms)

(benefit of HRT) > (cost of (risks of HRT))

2.3.9. In fact, hot flushes and night sweats are not associated with estradiol levels (Dhanoya et al. 2016). Menopausal vasomotor symptoms are predicted by other factors such as alcohol consumption (Sievert, Obermeyer, and Price 2006), diet (Herber-Gast and Mishra 2013), metabolic status (Tuomikoski and Savolainen-Peltonen 2017; Thurston et al. 2012), and season (Harlow et al. 2020). It appears determinants for each of night sweats and hot flushes are different from each other (Pérez-Alcalá et al. 2013) and subject to methodological and cultural factors (Melby and Lampl 2011; Melby et al. 2011). Note many authors distinguish reported 'bothersome' vasomotor symptoms *vs.* reported 'not bothersome' vasomotor symptoms. Please note also two of the studies mentioned in this paragraph are from the Study of Women's Health Across the Nation or (SWAN) initiated in 1996.[9]

2.3.10. In fact, around the world "…prevalence of [hot flushes and night sweating] varies widely and may be influenced by a range of factors, including climate, diet, lifestyle, women's roles, and attitudes regarding the end of reproductive life and aging…" (Freeman and Sherif 2007) and not estradiol.

2.3.11. The most comprehensive list of menopausal symptoms in (NICE NG23 2015) is on page 7 under "…Information and advice…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)…". Evidence underpinning is in (NICE HRT 2015) is the same 21 studies mentioned in paragraph 2.3.2. and the same is true for the other menopausal symptoms used in 'diagnosis' of menopause but under 'information and advice to the patient'.

(diagnosis of menopause) = (information to woman)

Vaginal dryness

[9] Two other SWAN studies are also notable here: (i) (Santoro et al. 2004) which found that "…women over age 42 who are premenopausal or in the early menopausal transition, there were important differences in the characteristics of cycles related to age, body mass index, and ethnicity. Comparisons to younger women indirectly support the inhibin hypothesis, which proposes that the initiating event in the menopausal transition is the loss of inhibin negative feedback on FSH secondary to a diminished follicular reserve…". However, all these hormones were *not* recommended to be measured by RCOG and NICE about ten years later and presumably to date; and (ii) (Gold et al. 2013) which found that "…natural FMP reflects a complex interrelation of health and socioeconomic factors, which could partially explain the relation of late age at FMP to reduced morbidity and mortality…" where FMP is final menstural period *and* natural final menstural period *and* early age natural final menstrual period *and* menopause.

2.3.12. As mentioned above, the information that HRT treats vaginal dryness is false because the same set of guidelines by RCOG and NICE also provide the information that vaginal dryness may/will resume on cessation of HRT.

2.3.13. There is no discussion of lubricants in the RCOG 'HRT' website for the nonprofessional woman user (RCOG HRT 2022a).

2.3.14. Products which may lubricate the vagina are presented to the nonprofessional woman in the RCOG 'menopause treatment' website as part of systemically administered HRT see paragraph 2.2.5. In other words, the purpose is to treat menopausal symptoms with a range of products some of which iatrogenically raise serum sex hormone level by local application, for example with a skin patch or by vaginal insertion of a ring.

2.3.15. The menopausal symptom of vaginal dryness is a urogenital symptom in (NICE HRT 2015):

under "…Recommendations…

…urogenital symptoms (for example, vaginal dryness)… Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen…" (*ibid*, pages 18-19).

Again under "…Recommendations… Explain to women that as well as a change in their menstrual cycle they may experience a variety of symptoms associated with menopause, including:… urogenital symptoms (for example, vaginal dryness)…" (*ibid*, pages 71-72)

under "Managing short-term symptoms…

…many women report other symptoms which can include: sleep disturbance; depression and mood changes; musculoskeletal pain; and urogenital symptoms. Sexual and urogenital problems around the menopause include vaginal dryness, dyspareunia and low libido – although these are complex symptoms, hormonal changes are often a contributing factor. It is less clear whether anxiety, irritability, palpitations, skin dryness and fatigue can be attributed directly to the menopause; fatigue, for example, may be due to sleep disturbance from night sweats…

Sexual disorders…Menopausal women may experience problems with sexual intercourse. This can be a complex issue that has both physical and psychological elements. The vaginal dryness resulting from urogenital atrophy can lead to pain during intercourse which can impact on libido. Loss of libido may also be a result of declining levels of oestrogen and testosterone as the ovaries fail; the lack of testosterone can be more marked in women who have their ovaries removed by surgery. Vaginal dryness tends to increase in severity with time since menopause. Topical treatment may be offered, both hormonal and non-hormonal.

The impact of severe menopausal symptoms on quality of life may be substantial and some women for whom HRT is contraindicated may choose to accept a degree of risk that might be considered by others to outweigh the benefits of menopausal hormone therapy (MHT). A woman should be fully informed and supported, and thereby empowered to make a decision that

best balances benefits to her when weighed against potential risks…" (*ibid*, page 73-74).

Subsequently, there is no vaginal dryness in NICE evidence analysed for menopausal symptoms see paragraph 2.3.8.

under "…Urogenital atrophy…

…It is estimated that symptoms caused by vulvovaginal atrophy can affect up to 50% of all postmenopausal women. The most common symptoms affecting the vulva and vagina include dryness, pain on intercourse, vaginal itching and vaginal discharge. There is increased vulnerability to inflammation, trauma and infection. Urogenital atrophy can also result in urinary symptoms, such as urgency to urinate and urinary tract infections…

…There is a range of treatments available, which include local oestrogen therapy (available in creams, vaginal ring and tablets) and non-hormonal options such as moisturisers and lubricants. Women may obtain non-hormonal preparations over the counter. Treatment should be started early before irreversible changes have occurred and needs to be continued to maintain benefits. It is vital that sufficient due care and attention is given to this condition to restore and maintain quality of life for increasing numbers of menopausal women in our ageing population….

… The aim of this review question was to assess both the safety and effectiveness of local oestrogen treatment and ospemifene (oral selective oestrogen receptor modulator) for vaginal atrophy (also known as genitourinary syndrome of menopause)…

…Nine [randomised clinical trials] in total were included in this review…The majority of evidence was of moderate to very low quality…

…The Guideline Development Group concluded that vaginal local oestrogens were found effective in relieving symptoms in the short term and long term for women in menopause with urogenital atrophy without risking the safety outcomes for this population…Recommendations…Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms…Consider vaginal oestrogen for women with urogenital atrophy in whom systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause…If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause….Explain to women with urogenital atrophy that: symptoms often come back when treatment is stopped; adverse effects from vaginal oestrogen are very rare; they should report unscheduled vaginal bleeding to their GP. Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen. Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy…" (*ibid*, pages 114-123). In other words, NICE evidence regarding vaginal dryness was analysed under 'urogenital atrophy' and not 'short-term

management'; there is no NICE evidence relating to the menopausal symptom of vaginal dryness.

(menopausal symptoms) = (woman) – (HRT)

(menopausal symptom) ⊂ {urogenital atrophy }

HRT = (systemic HRT) ± (local topical hormone application)

2.3.16. In fact, many practitioners use lube (which does not iatrogenically raise serum hormone level by local application, for example with a skin patch or by vaginal insertion of a ring).

2.3.17. In (NICE NG23 2015) for the health professional

under 'information and advice for the patient' "…urogenital symptoms (for example, vaginal dryness)…" see paragraph 2.3.11.

under "…Urogenital atrophy… Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen…"

under "…Terms used in this guideline… Urogenital atrophy…Thinning and shrinking of the tissues of the vulva, vagina, urethra and…bladder caused by oestrogen deficiency. This results in multiple symptoms such as vaginal dryness, vaginal irritation, a frequent need to urinate and urinary tract infections…"

(vaginal dryness) = (urogenital atrophy)

Sex drive

2.3.18. For the nonprofessional menopausal woman, sex drive is first lost in the RCOG 'HRT' website (RCOG HRT 2022a). Later, in the RCOG 'menopause treatment' website, sex was lost interest in (RCOG HRT 2022c) see paragraph 2.2.1.

2.3.19. To the best of my knowledge, the term 'sex drive' is not mentioned in (NICE HRT 2015), evidence underpinning what the nonprofessional woman and professional health user see.

under "…Managing short-term symptoms…" see paragraph 2.3.15. loss of libido is attributed to urogenital atrophy vaginal dryness…" and "…frequency of sexual intercourse as a measure of sexual function…" Later "…anxiety and frequency of sexual intercourse…Evidence on frequency of satisfying sexual intercourse, low mood (non-clinical depression)… limited data was found for the outcome of frequency of satisfying sexual intercourse, but testosterone (10 mg/day; gel) was found to significantly increase frequency…Quality of evidence on pair-wise comparisons for the outcomes of low mood, anxiety, frequency of sexual intercourse and musculoskeletal symptoms was often low or very low due to lack of information on randomisation methods and due to imprecision on estimates of effects.

under "…Urogenital atrophy…" see paragraph 2.3.15. "…The most common symptoms affecting the vulva and vagina include dryness, pain on

intercourse, vaginal itching and vaginal discharge…In terms of short-term symptoms, the measurement of vaginal pH, maturation index (for parabasal, intermediate and superficial cells) and women's subjective assessment of symptom improvement relating to atrophy, dryness, dyspareunia (painful intercourse), itching and discomfort were considered the most important outcomes…".

In other words, in NICE evidence

(sex drive or libido) = [(frequency of sexual intercourse) - (urogenital atrophy vaginal dryness) - (anxiety painful intercourse)]

[benefit of high frequency of sexual intercourse] ≥ [cost of (urogenital atrophy vaginal dryness) + (anxiety painful intercourse)]

2.3.20. In fact, sex is arguably the most profound experience dominating the psyche.[10]

2.3.21. For the healthcare professional in (NICE NG23 2015)

under "…Information and advice [to be given to the patient]…sexual difficulties (for example, low sexual desire)…" see paragraph 2.3.11.

under "…Altered sexual function…Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective. In November 2015, this was an off-label use. See NICE's information on prescribing medicines…" page 9.

under "…Context… 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…" (NICE NG23 2015) page 27.

(Low sex drive or libido) = (HRT) + (testosterone)

Stress incontinence (leaking urine when you cough or sneeze)

2.3.22. In (NICE HRT 2015)

under "…Development of the guideline…Relationships between the guideline and other NICE guidance…Related NICE guidance…Condition-specific…urinary incontinence (2013) NICE clinical guideline 171…"

also under 'information and advice to patient' discussed later.

[10] For a start the author recommends *Envy and Gratitude* by Melanie Klein, *Four Chapters on Freedom: Commentary on the Yoga Sutras of Patanjali* by Swami Satyananda Saraswati, and *Switch Bitch* by Roald Dahl.

In other words, there is no NICE evidence underpinning stress incontinence as a menopausal symptom.

(menopausal symptoms) = (woman) – (HRT)

[menopausal symptom) ⊂ { urinary incontinence}

To the best of my knowledge, stress/urine incontinence is not mentioned in the guideline for health professional users (NICE NG23 2015).

(menopausal symptom) ∈ (urogenital atrophy)

Bone thinning (leading to osteoporosis and fractures)

2.3.23. In (NICE HRT 2015)

under "…Managing short-term symptoms…" see paragraph 2.3.8.

under "…Osteoporosis…

…Osteoporosis is a skeletal disorder characterised by compromised bone strength that predisposes a woman to an increased risk of fracture, causing substantial pain, severe disability and a reduced quality of life…

…The aim of this review was to identify whether HRT use modifies the risk of developing osteoporosis. Further subgroup analyses were predefined in the protocol based on the effect of different durations of HRT treatment, age of HRT initiation, different HRT treatments and the time since treatment was discontinued.

Study designs included for this question were RCTs and comparative cohort studies. Only cohort studies which included appropriate adjustment for potential confounders (as outlined in the protocol) in their analysis were included.

Different types of fractures were prioritised by the Guideline Development Group to be the focus of this review: any fracture; any osteoporotic fracture; any non-vertebral fracture; hip fracture; vertebral fracture; wrist fracture.

For full details see the review protocol in Appendix D.

…Forty-one studies were included in this review…The Guideline Development Group considered different types of fragility fractures (such as any fracture, vertebral and non-vertebral, hip, wrist and osteoporotic) as the most important outcomes to answer this review question…

…The Guideline Development Group concluded that current use of HRT treatment compared with non-use for women in menopause is associated with a significantly lower risk of fragility fracture and this lower risk is preserved when HRT is discontinued, although magnitude of difference between groups is smaller. Age and HRT duration may not produce any change in the direction of these conclusions…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…" (NICE HRT 2015) pages 173-186.

In other words, (osteoporosis) = (fractures)

(menopausal symptom) ⊂ {osteoporosis}

2.3.24. In fact, osteoporosis is an radiological finding which may predispose a patient to fractures, along with many other well documented factors such as obesity and as noted and not corrected for by NICE during evidence processing. In fact, the only predisposing factor for osteoporosis in NICE evidence processing is not taking HRT.[11]

2.3.25. In (NICE NG23 2022) for healthcare professionals:

"…Loss of muscle mass and strength…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…

… 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…

…Managing premature ovarian insufficiency…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 HRT is not a contraceptive…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…

…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 hormonal contraceptives, HRT and androgens; the long-term impact of premature ovarian insufficiency on bone density and fracture, and cardiovascular and cognitive health; the long-term risk of cancer, which can be determined by linking with relevant cancer and mortality registries…

Using table 3, explain to women that their risk of fragility fracture is decreased while taking HRT and that this benefit: is maintained during

[11] "…Different comparisons of HRT use were described in the included studies: women who had ever used HRT ('ever users', consisted of both current and/or past users) were compared to women who had never used HRT ('never users'); current HRT users were compares to never users; and current users were compared to women not currently using HRT ('no current use'). Where relevant, this has been described in the GRADE tables. Similarly, where subgroup analysis was conducted regarding the age of participants, duration of use and time since stopping HRT this analysis has been presented…" (NICE HRT 2015) page 182.

treatment but decreases once treatment stops; may continue for longer in women who take HRT for longer…

Table 3: no available RCT data, cohort data included

(premature menopause) ∈ (menopausal symptoms)

(menopausal symptom) ∈ (osteoporosis)

(menopausal symptom) ∈ (sarcopenia)

(osteoporosis) = (fractures)

(HRT) ± (oral contraception) = (decreased risk of osteoporosis and CVD)

(cost of informing women about exercise) > (benefit of exercise on osteoporosis)

Anxiety and low mood

2.3.26. Anxiety and low mood are used loosely in (NICE HRT 2015) with *hot flushes* and *sex drive* discussed above.

2.3.27. In healthcare professional guideline (NICE NG23 2015) page 33 under "…Psychological symptoms…Consider HRT to alleviate low mood that arises as a result of the menopause…Consider CBT to alleviate low mood or anxiety that arise as a result of the menopause…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)…"

(anxiety low mood) ∈ (menopausal symptoms)

(anxiety low mood) ∈ (sex drive or libido)

2.3.28. In (NICE NG23 2022):

"…Psychological symptoms…Consider HRT to alleviate low mood that arises as a result of the menopause…Consider CBT to alleviate low mood or anxiety that arise as a result of the menopause…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)…

(menopausal symptom$_a$) ∈ (depression)

[(anxiety low mood) + (menopausal symptoms)] = [(HRT) ± (CBT)]

[(menopausal symptoms) – (depression)] = [(HRT) – (SSRIs)]

No hormone tests required for menopause diagnosis

2.3.29. This is true only in the absence of premature menopause in (NICE HRT 2015):

under "…Introduction…

…Menopause is a biological stage in a woman's life when she is no longer fertile and is marked by the cessation of menstruation. A woman is defined as postmenopausal from 1 year after her last period. The changes associated with menopause and the perimenopause (the years leading up to the menopause) occur when ovarian function diminishes and ceases. This includes the cessation of both egg (oocyte) maturation and sex hormone (principally oestrogen and progesterone) secretion.

Men continue to produce sperm into old age, but women have a finite number of oocytes at birth and the quantity declines with each menstrual cycle. The menopause is characterised by the eventual depletion of the oocyte store and cessation of menstruation. Menstrual cycle irregularity often occurs before periods stop completely.

Most tissues contain oestrogen receptors through which the hormone exerts its effects. The most immediate changes resulting from reduced oestrogen levels are evident in the regulation of the menstrual cycle. However, oestrogen depletion associated with the menopause has many other effects on the body – for example causing vasomotor, musculoskeletal, urogenital and psychological symptoms. It has also been shown to have an impact on the function of other systems in later life, including bones and the cardiovascular system. Oestrogen depletion explains some of the differences in the incidence of osteoporosis between men and women.

Perimenopause – also called the menopausal transition or climacteric – is the interval in which a woman has irregular cycles of ovulation and menstruation before the menopause. Within the UK population, the mean age of the natural menopause is 51 years, although this can vary between groups of different family origin.

Premature ovarian insufficiency (also known as premature ovarian failure or premature menopause) is usually defined as menopause occurring before the age of 40. It can occur naturally or iatrogenically (that is, as a result of treatment). Premature ovarian insufficiency (POI) and early perimenopause (menopause between the ages of 40 and 45) are associated with an increased risk of mortality, and with serious morbidity including cardiovascular disease (CVD), neurological disease, psychiatric disorders and osteoporosis. Lower socioeconomic status has been associated with POI…" (NICE HRT 2015) page 11.

under "…Guideline summary…

…Take into account the woman's clinical history (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency…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…Do not diagnose premature ovarian insufficiency on the basis of a single blood test…Do not routinely use anti-Müllerian hormone testing to diagnose premature ovarian insufficiency…If there is doubt about the diagnosis of premature ovarian insufficiency, refer the woman to a

specialist with expertise in menopause or reproductive medicine…Offer sex steroid replacement with a choice of HRT or a combined hormonal contraceptive to women with premature ovarian insufficiency, unless contraindicated (for example, in women with hormone-sensitive cancer)…Explain to women with premature ovarian insufficiency: the importance of starting hormonal treatment either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated); that the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40; 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 HRT is not a contraceptive….Give women with premature ovarian insufficiency and contraindications to hormonal treatments advice, including on bone and cardiovascular health, and symptom management…Consider referring women with premature ovarian insufficiency to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition.

…Research recommendations…What are the main clinical manifestations of premature ovarian insufficiency and the short- and long-term impact of the most common therapeutic interventions?...” (NICE HRT 2015) pages 14-26.

under “…Development of the guideline…what this guideline covers…Groups that will be covered…menopausal women (covering the perimenopause and postmenopause); women with premature ovarian insufficiency (irrespective of cause)…Key clinical issues that will be covered…diagnosis and management of premature ovarian insufficiency…Clinical issues that will not be covered…investigation of the cause of premature ovarian insufficiency in women presenting with primary amenorrhea…” (NICE HRT 2015) pages 26-30.

under “…Guideline development methodology…Health economic reviews were undertaken for review questions relating to short-term treatment and symptoms, the diagnosis of premature ovarian insufficiency (POI) and the treatment of urogenital atrophy in women with menopause-related vaginal/urogenital atrophy…” (NICE HRT 2015) pages 31-47

under “…Classification systems for the diagnosis of menopause…Other considerations…None of the Guideline Development Group members use a classification system in routine practice, although group members use standard questions – such as time since last period or age. However, a classification system could be useful in women with premature ovarian insufficiency (POI) as they often experience delays in diagnosis and treatment…”(NICE HRT 2015) pages 63-64.

Under “…Information and advice…Review question…What are the information needs for women in menopause? The aim of this review was to establish the most common areas of information needs for women in

menopause and the most effective ways of delivering this information. The focus population of this review question was perimenopausal and postmenopausal women. Information was presented separately for the following subgroups if data were available: women with premature ovarian insufficiency (POI); women with iatrogenic menopause, particularly due to cancer treatment or those at risk of cancer; women with natural menopause who present for symptom relief.

For the first part of the question, systematic reviews of qualitative studies, observational studies (ideally with large cohorts) and qualitative studies (natural history data, patient reported outcomes) were considered for inclusion. Areas of information needs were the focus of this part of the review question.

For the second part of the question, both randomised controlled trials (RCTs) and comparative cohort studies were selected for inclusion. Qualitative studies could also provide supplementary information. Any format of delivery of information was considered, including written and oral communication, and websites regarding menopause. Patient knowledge and number of visits to healthcare professionals were selected as the outcomes for this part of the review question.

For full details see the review protocol in Appendix D….” (NICE HRT 2015) page 65.

under “…Managing short-term symptoms…Recommendations…The recommendations in this section are not intended for women with premature ovarian insufficiency (see recommendations 61 to 63 for management of premature ovarian insufficiency)… (NICE HRT 2015) page 111.

under “…Long-term benefits and risks of hormone replacement therapy (HRT)…The group considered the spectrum of both randomised and cohort evidence and concluded that there was no strong evidence base to support the protective or negative effect of HRT on the risk of dementia for women experiencing a ‘normal’, as opposed to premature, menopause. There is some indication that there may a window of opportunity for lowering the risk of dementia with HRT use for women with specific preconditions, such as higher baseline risk if they have first-line relatives with dementia, or for women who have premature ovarian insufficiency (POI)…Research recommendations…There is a need for good-quality observational studies controlling for the effect of important confounders on how early HRT use affects dementia risk in women with early natural menopause, including women with premature ovarian insufficiency…” (NICE HRT 2015) pages 190-192.

Under “…Premature ovarian insuffiency…

…Introduction…Premature ovarian insufficiency (POI), formerly known as premature ovarian failure, means the loss of normal ovarian function, from a variety of causes, before the age of 40. Roughly 1 in 100 women in the UK have POI and often the diagnosis is extremely delayed. About 1 in 1000

women are affected under the age of 30 (Coulam 1986). There are 3 main identifiable causes of POI: genetic, autoimmune and iatrogenic (Yanuz 2014): Genetic conditions include: a strong maternal family history; 45,X,46,XXand46,XYPOI; POI associated with galactosaemia and FMR permutations; Women with an autoimmune predisposition may develop autoimmune POI, with or without other autoimmune diseases (diabetes mellitus, Addison's, thyroid). Women with iatrogenic menopause form an increasingly large group which includes women with benign disease and those having treatment for cancer (hormonal, chemotherapy and/or radiotherapy) which has brought about an early menopause. In most women the cause of an early menopause is unknown…

…Review question…What is the diagnostic accuracy of the following in the diagnosis of POI: cycle irregularity, vasomotor symptoms (VMS), FSH, AMH, AFC, inhibin B, inhibin A, oestrogen, ovarian volume?…Three studies…were included…The majority of evidence was low to very low quality as the included studies (case series) were small and at serious risk of bias…The group concluded that diagnosis of POI should be based on both assessing women's clinical history and elevated FSH levels…

…Relative values placed on the outcomes considered…The Guideline Development Group considered all the properties of diagnostic accuracy measurements required for decision-making: sensitivity, specificity, positive and negative likelihood ratio and area under the curve (AUC). The group considered the relative importance of having a high false positive and high false negative result in the diagnosis of POI and consequences for women's further clinical management. They concluded that it is equally important to have a correct positive diagnosis which can be used to initiate the appropriate treatment (see Section 12.3 on the management of women with POI) and a correct negative diagnosis that will prevent women from unnecessary distress and additional pharmacological treatment.

…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…

…Other considerations…The recommendations were based on both the interpretation of clinical evidence reviewed and on the expert opinion of Guideline Development Group members.

The lack of good quality clinical data makes it difficult to draw definitive conclusions about whether the OCP or HRT is a better choice for women with POI.

In the absence of long-term randomised prospective clinical trial data conclusions have to be drawn from clinical experience, limited short-term data and observational data.

The choice to use the OCP rather than HRT is often made from the pragmatic requirement for ongoing contraception and familiarity with the pill in young women. The group also noted how the same combination of

hormonal treatment may be available to the patient via alternative routes of administration, for example an interuterine device and patch.

The group considered the need to raise awareness among healthcare professionals and women with POI that the evidence presented on the long-term benefits and risks of HRT for women at the natural age of menopause (see Chapter 11, Sections 11.1–11.8) is not directly transferrable to this group of women, partly because the incidence of cardiovascular disease, breast cancer and osteoporosis is lower in women younger than 40 years.

Therefore, the group prioritised for further research the investigation of the long-term impact of the most common therapeutic interventions for POI to clarify their benefit: risk profile in these young women…

…Key conclusions…The Guideline Development Group concluded that: There is insufficient evidence to show whether HRT or the combined oral contraceptive pill is more effective for women with POI in treating short- or long-term sequelae; There is limited evidence on the beneficial role that HRT may have on reducing systolic or diastolic blood pressure compared with OCP.

…Recommendations…Offer sex steroid replacement with a choice of HRT or a combined hormonal contraceptive to women with premature ovarian insufficiency, unless contraindicated (for example, in women with hormone-sensitive cancer)…Explain to women with premature ovarian insufficiency: the importance of starting hormonal treatment either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated); that the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40; 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 HRT is not a contraceptive.

…Give women with premature ovarian insufficiency and contraindications to hormonal treatments advice, including on bone and cardiovascular health, and symptom management.

…Consider referring women with premature ovarian insufficiency to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition…" (NICE HRT 2015) pages197-211. In other words

(premature menopause) = [(age ≥ 40) ± (uterus) + (menopausal symptoms) + (2 elevated FSH samples 4-6 weeks apart)]

2.3.30. In guideline for health professionals (NICE NG23 2015)

see paragraph 2.3.5.

under "…Managing premature ovarian insufficiency…Offer sex steroid replacement with a choice of HRT or a combined hormonal contraceptive to women with premature ovarian insufficiency…unless contraindicated (for example, in women with hormone-sensitive cancer)…Explain to

women with premature ovarian insufficiency: the importance of starting hormonal treatment either with HRT or a combined; hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated); that the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40; 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 HRT is not a contraceptive…Give women with premature ovarian insufficiency and contraindications to hormonal treatments advice, including on bone and cardiovascular health, and symptom management…Consider referring women with premature ovarian insufficiency to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition.

(premature menopause) = [(age > 40) ± (uterus)] + (menopausal symptoms) + (2 elevated FSH samples 4-6 weeks apart)]

HERE THE NONPROFESSIONAL WOMAN IS DIRECTED FROM (RCOG HRT 2022a) TO (RCOG HRT 2022c)

Lifestyle changes

2.3.31. In (NICE HRT 2015) "…Give information to menopausal women and their family members or carers (as appropriate) that includes:…lifestyle changes and interventions that could help general health and wellbeing…Key clinical issues that will be covered…lifestyle advice…There are many different options for women, including lifestyle changes (see the NICE guidance on obesity)…" and in relation to sedentary lifestyle and strain on the musculoskeletal system.

(lifestyle changes) $\notin$ (HRT)

(obesity) $\subset$ {lifestyle changes }

2.3.32. In (NICE NG23 2015) page 6 "…lifestyle changes and interventions that could help general health and wellbeing…"

St John's wort

2.3.33. In (NICE HRT 2015) "…Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about: appropriate doses; persistence of effect; variation in the nature and potency of preparations; potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants)…

…None of the herbal treatments (ginseng, black cohosh, black cohosh plus St. John's Wort, St. John's Wort plus Chaste, pycogneal) included in the evidence basis was found to be significantly better than placebo on reducing either anxiety or low mood for menopausal women. The quality of this evidence ranged from moderate to very low quality…" and regarding cost-

effectiveness for St John's wort for menopause in breast cancer survivors, and see paragraph 2.3.8.

(St John's wort) $\not\subset$ (HRT)

2.3.34. In (NICE NG23 2015) page 10: "…Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about: appropriate doses; persistence of effect variation in the nature and potency of preparations; potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).

(breast cancer) = (no St John's wort)

Black cohosh

2.3.35. In (NICE HRT 2015):

see paragraph 2.3.8.

"…Explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms. However, explain that: multiple preparations are available and their safety is uncertain; different preparations may vary; interactions with other medicines have been reported…Key clinical issues that will be covered…herbal preparations (including black cohosh and red clover)…Isoflavones and black cohosh were also shown to be more effective than placebo in relief of VMS for women with a uterus, but not significantly better when compared with combined oestrogen plus progestogen…

…The health economic model developed for this guideline suggested that transdermal HRT was the most cost-effective treatment for women with menopausal symptoms with and without an intact uterus, albeit with some uncertainty, especially at the lower end of the symptom severity spectrum, with black cohosh slightly more cost effective at a frequency of 2 hot flushes per day. However, it should be noted that women with less severe menopausal symptoms are less likely to seek medical treatment for their symptoms.

These results were driven by the network meta-analysis on the outcome of frequency of vasomotor symptoms in which black cohosh and transdermal HRT had the best relative treatment effects and were the only 2 treatments significantly better than placebo at a 5% level of statistical significance. Black cohosh had the second lowest mean ratio for (relief of) vasomotor symptoms for women with a uterus and the second highest probability of being the most effective treatment.The probabilistic sensitivity analysis for the economic modelling, which gave the probability of black cohosh being the most cost-effective treatment, reflected the same direction of results. However, at the lower end of severity of symptoms, black cohosh had a higher probability of being cost effective because of its lower cost relative to non-oral oestradiol and progestogen and lower risk of breast cancer and VTE. However, as symptom severity increases (where clinical effectiveness

becomes a more important driver of cost effectiveness), the probability of black cohosh being the most cost-effective treatment declines…

…There is also some evidence to suggest that isoflavones and black cohosh may be beneficial for [reducing the frequency of hot flushes in women with a uterus]…" (NICE HRT 2015) in order of appearance.

(black cohosh) ∉ (HRT)

(benefit of black cohosh) > (benefit of HRT)

(risk of black cohosh) + (cost of standardizing black cohosh treatment) > (cost of HRT) + (benefit of HRT)

2.3.36. In (NICE NG23 2015) page 8 "…Explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms. However, explain that: multiple preparations are available and their safety is uncertain; different preparations may vary; interactions with other medicines have been reported…"

(risk of black cohosh and isoflavones) > (benefit of black cohosh and isoflavones)

Isoflavones

2.3.37. These are discussed loosely with black cohosh and/herbal remedies as above.

(isoflavones) ∉ (HRT)

2.3.38.

Acutherapy

2.3.39. Under "…Key clinical issues that will be covered…acupuncture…" (NICE HRT 2015) page 28.

(acutherapy) ∉ (HRT)

2.3.40. To the best of my knowledge, acupuncture is not mentioned in (NICE NG23 2015).

Homeotherapy

2.3.41. To the best of my knowledge, homeotherapy is not mentioned neither in (NICE NG23 2015) nor in (NICE NG23 2015).

(homeotherapy) ∉ (HRT)

Aromatherapy

2.3.42. To the best of my knowledge, homeotherapy is not mentioned neither in (NICE NG23 2015) nor in (NICE NG23 2015).

(aromatherapy) ∉ (HRT)

Bioidentical hormones

2.3.43. Safety unknown in both (NICE NG23 2015) nor in (NICE NG23 2015).

(bioidentical hormones) ∉ (HRT)

Clonidine or gabapentin and cognitive behavioural therapy

2.3.44. In (NICE HRT 2015) page 108: "…The group acknowledged how the selection of outcomes for this review and, in particular, the exclusion of evidence because of the way the outcomes were reported (for example frequency as opposed to intensity of VMS intensity) was a limitation of the review which particularly impacted the evaluation of non-hormonal (such as clonidine) and non- pharmacological treatments (such as CBT). All of these intereventions (non-hormonal and non-pharmacological) were included in the clinical searches and were considered for inclusion in the NMA as discussed in Appendix K. However, most of these interventions (such as clonidine, CBT or hypnosis) were subsequently excluded from the NMA and therefore their relative effectiveness on relieving short-term symptoms for women in menopause could not be estimated along with the other interventions included in the NMA. In the absence of this data, the group recognised the importance of these treatments in the management of some women with menopause, especially if they don't wish to be treated with pharmacological treatments (such as HRT) and therefore highlighted them also in the recommendations in the Information and advice section of the guideline (see Chapter 7)…".

(clonidine, gabapentin, CBT) ∉ (HRT)

2.3.45. In (NICE NG23 2022) "…Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone…"

Testosterone

2.3.46. In (NICE NG23 2015):

see sex drive paragraph 3.3.19

"…Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective…At the time of publication (November 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.

…Tibolone belongs to the group of normethyltestosterone progestogen derivatives: it has metabolites that exhibit estrogenic, progestogenic and androgenic effects, and has been in clinical use since the early 1990s for treatment of menopausal symptoms…

…Both studies reporting results for the outcome of frequency of sexual intercourse included the majority of women with surgical

menopause…There is evidence that testosterone may increase the frequency of sexual episodes for women in surgical menopause when compared with placebo…"

(testosterone) = (increased frequency of sexual intercourse)

HRT = (estrogen) ± (progesterone) ± (testosterone)

2.3.47. In (NICE NG23 2022) "…Altered sexual function…Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective…"

[(low sex drive libido) + (HRT without testosterone)] = (HRT with testosterone)

Long-term risks and benefits of HRT

2.3.48. In (NICE HRT 2015):

under "…Long-term benefits and risks of hormone replacement therapy (HRT)…The aim of this review was to determine the effect of HRT on the risk of developing [venous thromboembolism or] VTE for women in menopause…Two outcomes were prioritised by the group: risk of developing VTE (including DVT and PE); mortality related to VTE…Seven RCTs comparing some form of HRT with placebo were included in this review…

…Moderate to very low quality of evidence from 7 RCTs including 34,379 women showed a significantly increased risk of VTE with current oral use of any HRT when compared with placebo. The same result was found when the role of either oestrogen alone or oestrogen plus progestogen was examined in comparison with placebo by 2 RCTs (total 11,756 women) and 4 RCTs (total 21,301 women), respectively…Findings on the risk of VTE in relation to duration of HRT use were mixed. Moderate quality evidence from a single RCT including 4385 women showed a significantly increased risk for up to 1 year duration and more than 5 years duration (evidence from 2 RCTs including more than 20,000 participants). However, low quality evidence from 4 RCTs (total 2479 women) showed no significant difference between those who were on HRT for between 1 and 5 years when compared with those on placebo…

…When the subgroup of women aged 50–59 at baseline was examined, low quality evidence based on over 5000 women from an RCT showed an increased risk in VTE for women taking oestrogen plus progestogen in comparison with those in placebo group, whereas findings based on over 3000 women from another RCT showed no significant difference in VTE risk between oestrogen alone use and placebo (very low quality evidence).

…Time since menopause…One RCT with a subgroup analysis of women age 50–59 years showed that among those who have initiated oestrogen plus progestogen within 10 years since menopause, there was a significant increased risk of VTE when compared with the placebo group (moderate quality evidence). However, very low quality evidence from the same RCT showed that the risk of VTE was not significantly different between users

of oestrogen alone and placebo groups…Evidence statements for comparative cohort studies Current HRT use…Moderate to very low quality evidence from 3 cohort studies (sample size ranged from 600 to 60,000 women with menopause) found a significantly increased risk of VTE in current HRT users compared with the no treatment group.

…Moderate quality evidence from a large cohort study (about 500,000 women) showed a significantly increased risk of VTE in oral HRT users with a duration of 2 years or less compared with non-users, but this difference was not found to be significant when transdermal HRT users were compared with non-users…

…Relative value placed on the outcomes considered…The Guideline Development Group considered VTE a critical long-term outcome for evaluating the effect of HRT on women. VTE is associated with long-term morbidity via an increase in pulmonary embolus and is also associated with increased mortality. This complication has been widely reported as being associated with use of sex steroid hormones (such as the combined oral contraceptive pill) which impact the hepatic synthesis of coagulation factors and thus increase the risk of clotting.

The group followed the principles established in the NICE guideline on patient experience in adult NHS services regarding the presentation of information to personalise risks and benefits as far as possible. For that purpose the use of absolute risk is preferred rather than relative risk. Information provision of all aspects of the benefit/risk ratio of HRT regarding both the short term and the long term is of paramount importance for women's decision- making regarding the choice of treatment for menopausal symptoms.

…Consideration of clinical benefits and harms…Overall, evidence from both RCTs and observational studies was largely consistent with regard to the increased risk of VTE associated with current oral HRT use compared with non- use for women in menopause.

The Guideline Development Group concluded that current oral HRT use was associated with a significant increase in risk of developing VTE compared with non-use. Conversely, the risk of VTE was not found to be significantly different with transdermal HRT use compared with non-use. This difference in the risk of VTE between oral and transdermal routes of HRT was supported by data from studies of both designs. In particular, subgroup analyses of observational data showed that this trend was the same whether the duration of HRT use was less than 2 years, less than 5 years or more than 5 years, and whether women started HRT use either before or after age 50 years. Furthermore, when oral and transdermal HRT were directly compared in 2 observational studies, both studies found a significantly increased risk of VTE among those taking oral HRT compared with those on transdermal HRT. Therefore, the group concluded that the information given to women prior to HRT use should explain that the risk of VTE is increased with oral HRT use whereas this is not the case for transdermal HRT. However, the group still wanted to draw attention to

women's baseline risk of VTE and the recommendation explicitly states that transdermal HRT does not not further increase the risk of VTE above the individual baseline risk. Furthermore, due to the well-known VTE risk associated with obesity, the group emphased that the use of transdermal HRT is not contraindicated for those with a high BMI (over 30 kg/m2).

The evidence showed that the increase in the VTE risk occurs rapidly after starting HRT and continues until treatment is discontinued. Evidence from randomised participants showed a significantly increased risk of VTE within the first year of HRT use, while observational data on oral HRT also reported the same effect direction for up to 2 years of HRT treatment.

For women who had experienced previous episodes of VTE, observational evidence found no significant difference between HRT users and non-users. However, the group considered that there may be special considerations for this set of menopausal women before they start HRT and concluded that a referral to a haematologist should be offered.

Findings for different types of progesterone and progestogens in combined HRT were inconclusive. Some observational studies showed an increased risk for some specific preparations of progesterone or progestogen when combined with oestrogen, while other studies found no significant difference. Therefore, the group decided not to differentiate the direction of their decision-making based on HRT type.

Besides the general inconsistency in evidence, the group also noted the large sample sizes of some included studies. For example, 1 of those studies included more than 500,000 women. The group considered that although VTE was a significant side effect, it was relatively uncommon in women of menopausal age. It was found that 9 more per 1000 women (95% confidence interval [CI] 2 to 32 more) treated with HRT (oral or transdermal) may develop VTE within the first year of use, and this absolute risk would increase to 10 more per 1000 women (95% CI 5 to 13) for the duration of 5 years of use.

Consideration of economic benefits and harms…VTE is expensive to manage and treat and is associated with significant morbidity and mortality. VTE is recognised as a potential adverse event arising from oral HRT treatment and therefore it was important to consider it as part of an overall trade-off of risks and benefits of therapy. This trade-off was done formally through an economic evaluation reported in Appendix L, although the analysis did not find that VTE outcomes were an important determinant of cost effectiveness.

Quality of evidence…Evidence from this review was assessed as being of moderate to very low quality.

Other considerations…The recommendations were based on both the interpretation of clinical evidence and the expert opinion of Guideline Development Group members.

The group discussed the importance of well-known risk factors for VTE, such as age, genetic abnormalities, obesity, smoking and the presence of an inherited thrombophilia impacting on the clotting cascade with increase in coagulation (thrombophilias). They discussed how these should be taken into consideration when a prescription of HRT is considered. They also noted that some women with risk factors for VTE may be on anticoagulant therapy which means they should only be considered for HRT following specialist advice. The group considered that a referral should be made to a haematologist for all women with a significant increase in risk of DVT, for example a previous thromboembolic episode or a hereditary thrombophilia (Factor V Leiden). The decision whether to offer HRT or not to these women is complex and therefore the group decided that the involvement of a haematologist is necessary in order to contribute expertise to a woman's thrombophilia risk assessment before considering HRT unless she is already on anticoagulant therapy.

The group also discussed the management of women who use HRT and are considered for elective surgery. Since transdermal HRT has little or no impact on coagulation and is not associated with an increased risk of VTE, the group did not consider that there is a need for HRT to be discontinued prior to elective surgery, especially when the surgery is minor and will not involve immobility. However, the group felt that this is a discussion that should take place between the woman, her surgeon and her anaesthetist.

Key conclusions…The Guideline Development Group concluded that: Oral HRT (either oestrogen alone or oestrogen plus progesterone) increases the risk of VTE and this can occur immediately after starting HRT treatment.; There is no significantly increased risk of VTE in women using transdermal preparations compared with non-users.; The risk of VTE when using progesterone and the different progestogens may differ when combined with oestrogen.; The background risk of VTE increases substantially with age and this should be taken into consideration when HRT use is considered for women in menopause.; The increased risk of VTE disappears after HRT use has been stopped. 11.1.8 Recommendations

…Explain to women that: the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk; the risk of 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 population risk.

Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m2.

Consider referring 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…" (NICE HRT 2015) pages 132-139.

In other words,

[(high risk of VTE with HRT) + (low risk of DVT and PE)] > [risk with oral HRT] > [risk with transdermal HRT]

under "…Cardiovascular disease…What are the effects of HRT administered for menopausal symptoms on the risk of development of cardiovascular disease (CVD) (including stroke) in women at different stages of the menopause?... Five RCTs comparing some form of HRT with control or placebo group were included)…

…Very low quality evidence of a meta-analysis of 4 cohort studies with more than 70,000 participants showed a significant reduction in the risk of CHD between current HRT users and non-users.

However, a subgroup analysis of 2 cohorts of women younger than 55 years found no difference in the risk of CHD among current HRT users and non-users (very low quality evidence).

…For the outcome of IHD 1 cohort study found no significant difference in the risk of IHD among users of any route of HRT with a duration of 7 to 12 months compared with HRT users of less than 6 months' duration. The same direction of effect was found in users of any route of HRT with a duration of 1 to 2 years and 2 to 3 years. The quality of this evidence was low. Low to very low quality evidence that had the different routes of administration (oral, transdermal) supported the same conclusion.

For the outcome of death from IHD, CVD or CHD: Very low quality evidence from single cohort studies found no difference in the risk of IHD death in former HRT users aged 36–59 years compared with non-users. The same was found in former HRT users aged 60–64 years and for HRT users who initiated the treatment at the age of 45–54 years or 55–64 years; Timing of initiation of HRT since menopause was not found to impact on the previous finding that there is no difference in the risk of IHD death in women who initiated HRT use within 5 or 10 years since menopause compared with non-users.; Meta-analysis of 4 cohort studies showed a significantly lower risk of CVD death in current HRT users compared with non-users. The quality of evidence was low.; Meta-analysis of 4 cohort studies showed a significantly lower risk of CHD death in current HRT users compared with non-users. The quality of evidence was very low.; Very low quality evidence from 2 cohort studies found no difference in the risk of CHD death in current HRT users of more than 5 years' duration compared with non-users.

For the outcome of total stroke (generally including fatal and non-fatal, ischemic and haemorrhagic stroke in studies) low quality evidence from different cohorts comprising more than 50,000 participants showed: There was a significantly increased risk of total stroke in current HRT users compared with non-users.; There was no difference in the risk of total stroke in current HRT users with a duration of more than 2 years (2 cohorts) or 5 years (2 cohorts) compared with non-users. The quality of evidence was very low.; There was no difference in the risk of stroke among users of any route of HRT and with a duration of 7 to 12 months compared with HRT

users of less than 6 months' duration. The same was found in users of any route of HRT with a duration of 1 to 2 years. However, a significantly reduced risk of stroke was found in users of any route of HRT with a duration of 2 to 3 years, and of more than 3 years when compared with HRT users of less than 6 months duration. The quality of evidence was low.; One cohort study found a significantly reduced risk of stroke among users of transdermal HRT with a duration of 7 to 12 months, 2 to 3 years and more than 3 years when compared with HRT users of less than 6 months duration. However, among users of transdermal HRT with a duration of 1 to 2 years, no difference was found in the risk of stroke when compared with oral HRT users of less than 6 months' duration. The quality of evidence was low.

One cohort study found no difference in the risk of stroke among users of oral HRT with a duration of 7 to 12 months compared with HRT users of less than 6 months' duration. The same was found in users of oral HRT with a duration of 1 to 2 years, 2 to 3 years and more than 3 years. The quality of evidence was low to very low.

Health economics profile…No health economic search was undertaken for this guideline as the decision was made to prioritise short-term treatment. The review undertaken for this guideline of CHD related to HRT use found no convincing evidence that administration of HRT increases risk in women aged under 65 years. There was evidence that HRT increases the risk of stroke when administered orally, but the absolute risk was very small and therefore the clinical evidence from this review was not used to inform the model on short-term treatment.

…Evidence to recommendations…Relative value placed on the outcomes considered…The Guideline Development Group considered different types of CVD, such as stroke and MI, cardiac event composite scores, change in blood pressure and mortality from CVD as the most important outcomes for this review question. The group followed the principles outlined in the NICE Patient Experience guideline regarding the presentation of information to personalise risks and benefits as far as possible. For that purpose, the use of absolute risk is preferred rather than relative risk. Information provision of all aspects of the benefit/risk ratio of HRT regarding short- and long-term consequences of treatment is of paramount importance for women's decision-making regarding the choice of treatment for menopausal symptoms (linked to other long-term symptom reviews).

…Consideration of clinical benefits and harms…The population included in this review was women who have initiated treatment with HRT before age 65 years. Randomised evidence from several thousand women aged between 45 and 58 years consistently showed that the risk of stroke and MI is not significantly different between menopausal women who received HRT (either as oestrogen alone or as a combination of oestrogen plus progestogen) and those who received no treatment and the group decided to recommend that menopausal women and healthcare professionals involved

in their care understand that HRT doesn't increase the cardiovascular disease risk when started in women aged under 60 years.

Subgroup analyses of RCT data also showed an absence of harm for those women being treated with either oestrogen alone or oestrogen plus progestogen and this was preserved independently of the timing of initiation of HRT (within 2, 4, 5 or 10 years since menopause) and duration of HRT. This result also remained 6 or 8 years after termination of HRT.

Evidence from observational studies revealed similar conclusions to those drawn from RCTs, although more information was provided for specific subgroups (for example women with pre-existing heart disease), different routes of HRT administration and different HRT durations.

The group placed importance on the following results from the observational studies when they were drafting the recommendations: The risk of CHD was significantly lower for women using HRT compared with no treatment across different follow-up periods (4, 10, 16 and 20 years) and different HRT durations (1, 2, 5 or 10 years) although the risk seemed to significantly increase in current users with pre-existing heart disease.; Conflicting results were found as to whether the risk of CVD or CHD is reduced or is similar in current HRT users compared with non-users.; Some observational data found that the risk of stroke may be higher for women aged under 55 years who are on HRT compared with non-users, whereas other evidence found no difference in the outcome of stroke among users of any route of HRT with different duration of use and long-term follow-up (16, 20 years) when compared with non-users.; Weak data suggesting transdermal HRT administration may be associated with a lower risk of stroke than oral.

The group discussed the role of age in development of heart disease: CHD risk rises for everyone as they age, but for women, specifically, cardiovascular symptoms can become more evident after the onset of menopause. Although menopause does not cause CVD, there may be associated risk factors (such as smoking, poor diet, lack of exercise) that increase the risk of CVD around the time of menopause. The group considered in detail the synthesis of evidence and they concluded that there is no clear evidence of harm in terms of CHD or stroke in menopausal women who are taking HRT and aged under 65 years when HRT is terminated. Therefore, there is enough evidence to support healthcare professionals in advising women of the absence of or low risk in CVD outcomes associated with the use of HRT. In addition, although there were limited data indicating that there may be a significant increase in CHD found in current HRT users with pre-existing conditions compared with non-users, the group did not feel that this evidence was compelling enough to draft a negative recommendation for information giving.

Based on UK data, the baseline risk of CVD and stroke is low at 26.3 per 1000 and 11.3 per 1000 (Weiner 2008) respectively, over a period of 7.5 years (please see further details in Methods section how this risk was

calculated). This increases with age but is not significantly increased by the use of HRT.

…Consideration of economic benefits and harms…The evidence shows that HRT increases the risk of stroke of women who are in menopause. However, the absolute risk is very small and therefore the economic benefits and harms are limited. There is a suggestion that transdermal preparations have less impact on the risk of stroke than oral preparations.

…Quality of evidence…The majority of RCT evidence was low to very low quality, largely due to high risk of bias (mainly due to unblinding of study design) and the lack of confidence in the direction of effect size (imprecision). The WHI data, which contributed substantially to the RCT evidence base, had some design limitations; namely that the study included a group of healthy menopausal women with a high baseline BMI (35–40% of this group had BMI of 30 kg/m2 or over) and was terminated earlier than expected due to high prevalence of side effects. In addition, a proportion of the women included in the trial had initiated treatment outside the study's protocol (for example 9.1% in the placebo arm were using HRT) and 36% had previous HRT experience. Thus the greatest concern in using the WHI study was the external validity of the estimates given by the characterisation of the present study population. Furthermore, the information from the post-intervention period is unblinded. Several post-hoc analyses have been included for the presentation of the relevant evidence and the results of these analyses should be interpreted with caution due to lack of statistical power in these type of analyses. However, the sample size of this trial was sufficiently large to allow clinically relevant conclusions.

The majority of observational evidence (cohort studies) was assessed as being of very low quality. The main methodological limitations of these studies were the difference in baseline characteristics between the HRT and no treatment arms, the highly selective approach of the included population (for example the Nurse's Health Study included only nurses (potentially a healthy cohort) and the serious heterogeneity and imprecision observed in some of the results. Given that these data were observational and the role of confounding factors is important in the estimates of effects, evidence was downgraded if the results were not adjusted for the most relevant confounders (such as age and HRT duration).

Other considerations…The recommendations were based on both the interpretation of clinical evidence reviewed and on the expert opinion of the Guideline Development Group members.

The group discussed how this review did not consider any potential differences in outcome related to different types and dosage of HRT, although there was weak evidence suggesting that transdermal preparations may be associated with a lower risk of stroke than oral, consistent with the finding of lower VTE risk. The expert opinion of the group suggests that there may be differential effects and further research in this area is needed.

This review question looked at the impact on the risk of CVD of HRT use, duration, timing since stopping and age, but did not consider any potential differences in outcome related to the different formulations or the type and dosage of HRT in the preparations, although the clinical experience of the group members suggests that there may be differential effects and further research in this area is needed.

Although the group concluded that menopausal women should be informed that the risk of CHD associated with HRT use is low or minimal, they highlighted the need for all women around the age of menopause to have their personal cardiovascular risk reviewed on an ongoing basis in line with the NICE guideline on lipid modification.

…Recommendations…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…Be aware that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed…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….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 population risk of stroke in women aged under 60 years is very low (see table 2)…" (NICE HRT 2015) pages 139-152.

In other words,

[absolute risk of CVD with HRT] > [relative risk of CVD with HRT] ≥ [risk of stroke with HRT] > [risk of CVD with oral HRT] > [risk of CVD with transdermal HRT]

under "…Development of Type 2 diabetes…What are the effects of HRT administered for menopausal symptoms on the risk of developing type 2 diabetes (T2DM)?... Four studies were included for this review question…Low quality RCT evidence from almost 10,000 women aged 50–59 showed that there was no significant difference in the risk of T2DM between those who were current users of conjugated equine oestrogen compared with placebo at 7 years follow-up…The Guideline Development Group concluded that HRT administration is not associated with an increased risk of developing T2DM…

…Consideration of clinical benefits and harms…Although evidence from randomised studies showed no significant difference in risk of developing T2DM associated with HRT compared with placebo, evidence from large cohort studies found that current HRT users have a significantly lower risk of T2DM compared with non-users. This protective effect of HRT on the

risk of developing T2DM seems to disappear when the HRT treatment stops, as was found when data were compared between past HRT users and non-users. Data from post hoc subgroup analyses of different durations of HRT consistently indicated a protective effect of HRT on T2DM risk. Route of administration also did not seem to change HRT's protective effect against T2DM. The group discussed the contrast of this result with the data for the combined oral contraceptive which contains higher concentrations of more potent sex steroids…" (NICE HRT 2015) pages 153-157.

In other words, [cessation of HRT] = [increased risk of T2DM]

under "…Type 2 diabetes management – control of blood sugar…What impact does administration of HRT have on diabetes/glycaemic levels in those with T2DM?… Five RCTs, 4 of which were parallel RCTs…and 1 crossover RCT…were included…The quality of evidence included for this question was considered to be low to very low. The included trials had very small sample sizes (the largest included 50 women in total) and there were serious concerns about the risk of bias (selection, performance and attrition). Imprecision was also a quality domain commonly and negatively affected. The timing of outcomes reported (3 to 6 months) was also not long enough to allow the demonstration of an effect between the comparisons (HRT or no HRT use). Not all studies have provided information about whether the blood glucose testing was conducted under fasting conditions….

…The only evidence found was for the outcomes of HbA1c and blood glucose measurements and for postmenopausal women…

…The recommendations were based on both the interpretation of clinical evidence and on the expert opinion of Guideline Development Group members….

…Key conclusions…The Guideline Development Group concluded that HRT does not exert a negative or positive impact on diabetic/glucose control for women with T2DM. However, the evidence base for this topic had flaws and the generalisation of results should be interpreted with caution.

…Recommendations…Ensure that women with type 2 diabetes and all healthcare professionals involved in their care are aware that HRT is not generally associated with an adverse effect on blood glucose control…Consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed…" (NICE HRT 2015) pages 157-162.

In other words,

[measuring fasting blood glucose + HbA1c] = [improved outcome for women on HRT]

(cost of measuring blood glucose) > [(cost of HRT-related T2DM) + (risk of HRT-related T2DM)]

under "…Breast cancer…What are the effects of HRT administered for menopausal symptoms on risk of developing breast cancer?... Four RCTs comparing some form of HRT with placebo were included in this

review…Low to very low quality evidence from both randomised and comparative cohort studies was considered for this review question and evidence was presented by HRT type when data were available…

"…Low to very low quality evidence from 4 RCTs (with sample sizes ranging from 1000 to more than 5000 postmenopausal women) showed that the risk of breast cancer was not significantly different between those who had received hormonal replacement treatment and those who had not...

However, evidence from 3 RCTs, including the post-intervention follow-up, presented mixed results. Very low quality evidence from 1 RCT with more than 1000 participants found no significant difference between any HRT use and the control group during the 16-year treatment and follow-up period. The same was found by another RCT examining the effect of oestrogen in comparison with placebo during its 12.6 years treatment and follow-up period (very low quality evidence). Low quality evidence from 1 RCT (for the subgroup of over 5000 women aged 50–59 years) found that the risk of developing breast cancer is significantly higher for women who received oestrogen plus progestogen compared with those on placebo during 13 years of treatment and follow-up but not for women on oestrogen alone…

…Evidence statements for cohort studies Type of HRT (duration not specified)…Several cohorts of over 200,000 postmenopausal women found that those who received oestrogen alone or oestrogen plus progestogen had a significantly higher risk of breast…

…Inconsistent results from several cohorts were found to reveal a trend regarding the impact of the duration of HRT use on the development of breast cancer…

…Relative value placed on the outcomes considered…The Guideline Development Group considered the risk of breast cancer and mortality from breast cancer as the most important outcomes for answering this review question. The group followed the principles set up in the NICE Patient Experience guideline regarding the presentation of information to personalise risks and benefits as far as possible. For that purpose the use of absolute risk is preferred rather than relative risk. Provision of information provision on all aspects of the benefit/risk ratio of HRT regarding short- and long-term consequences of treatment is of paramount importance for women's decision-making regarding the choice of treatment for menopausal symptoms (see section 11 on long-term benefits and risks of HRT).

…Consideration of clinical benefits and harms…The included evidence from both randomised and cohort studies showed that there may be risk of developing breast cancer during treatment associated with oestrogen plus progestogen compared with no HRT use, but this risk does not seem to be the same for those women treated with oestrogen or progestogen taken alone.

More specifically, the WHI study found that in postmenopausal women aged 50–59 years treated for around 3.2 years with oestrogen plus progestogen the absolute risk of developing breast cancer was 8 more

women per 1000 (95% confidence interval [CI] 1 fewer to 17 more) compared with women on no HRT treatment. However, this higher absolute risk was not observed in the other 2 RCTs which included smaller sample sizes and longer follow-up periods. The cohort studies also found that the absolute risk of developing breast cancer was significantly higher in women who ever used oestrogen and progestogen compared with those who never used it (29 more per 1000 [95% CI 5 to 73), while the results from the current users of oestrogen plus progestogen compared with women who had never used it moved in the same direction (17 more per 1000 [95% C.I 14 to 20]).

Evidence from observational studies showed that when HRT was used for more than 5 years, the risk of breast cancer may be increased but this associated risk seems to disappear after HRT is stopped. More specifically, it was found that 23 more women per 1000 women (95% C.I 8 to 45) treated with HRT for 5 to 10 years may develop breast cancer compared with those who have never used HRT, and this absolute risk increases to 47 more per 1000 (95% C.I 20 to 91) for a duration of HRT use of 10 to 14 years. Most of the women in the included studies started HRT when aged between 50 and 59 years and the group discussed how this would represent the majority of women starting HRT in the UK, as it is unusual for women to start using HRT after age 60. The WHI study also included women with prior HRT exposure, but it was not possible to further explore a duration HRT effect on risk of breast cancer given the limited presentation of data…

…Consideration of health benefits and resource uses…Breast cancer is expensive to manage and treat and has significant morbidity and mortality associated with it. As an adverse event arising from HRT use it is part of an overall trade-off of risks and benefits. This trade-off was assessed formally through an economic evaluation reported in detail in Appendix L…

…The recommendations were based on both the interpretation of clinical evidence reviewed and on the expert opinion of the Guideline Development Group members…

…Key conclusions…HRT with oestrogen and progestogen may be associated with an increased risk of breast cancer. Any increased risk of breast cancer associated with HRT is low and should be taken in the context of the overall benefit and risk ratio in using HRT for treating menopausal symptoms. In addition, this risk seems to be lost when HRT is discontinued, as demonstrated in the studies on the low risk of breast cancer for past HRT users.

… Recommendations…Using table 3, explain to women around the age of natural menopause that: the baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors; HRT with oestrogen alone is associated with little or no change in the risk of breast cancer; HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer;

any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT…" (NICE HRT 2015) pages 162-173.[12]

In other words,

(risk HRT-related breast cancer) < (cost of HRT-related breast cancer)

under "…Osteoporosis…" see paragraph 2.3.24.

under "…Dementia…What are the effects of HRT administered for menopausal symptoms on the risk of dementia?… The majority of included studies focused on dementia as a result of Alzheimer's disease… There is no strong evidence of either a risk or benefit from HRT use on dementia and in the absence of such evidence it is not possible to conclude what the economic benefits and harms are, if any…" (NICE HRT 2015) pages 186-192.

In other words [dementia] ∉ [HRT-related life]

under "…Loss of muscle mass ('sarcopenia')… Sarcopenia means loss of muscle mass and strength. It is not a disease or a syndrome but part of physiological ageing.…What are the effects of HRT administered for menopausal symptoms on the risk of developing sarcopenia?...A total of 7 studies were included in the review. Six were RCTs, of which 5 were double- blinded…and 1 was open-label…Only 1 prospective comparative cohort study was included…

… The Guideline Development Group assessed sarcopenia as the age-related loss of lean muscle strength and muscle mass which in turn affects balance, gait and overall ability to perform tasks associated with daily living. The group considered the change in muscle strength (knee extension torque and strength, flexion, handgrip strength and adductor pollicis) to be the most important outcome for their decision-making. Change in muscle mass was assessed using either cross-sectional lean tissue area or appendicular skeletal muscle mass.

[12] And "…For breast cancer, age-specific baseline incidence rates for women aged 45 to 79 in the UK in 2010 were taken from the Office of National Statistics (ONS) database. A limitation of using this statistic is that it includes women on HRT in addition to those not on HRT. However, it was considered to be the most reliable estimate available, as the proportion of women using HRT in the ONS estimate is relatively low and the group indicated that the recording of prior HRT use in many studies was unreliable. An overall annual rate for women aged 45 to 79 was calculated by weighting the age-specific incidence rates by the proportion of women of each age within the general population, as reported in the 2011 national census. This annual incidence was then multiplied by 7.5 to reflect the average length of follow-up in the studies included in the review, giving a baseline incidence over 7.5 years of 22.48 per 1000 women…" (NICE HRT 2015) pages

… For this review question the group focused on the impact of HRT on the risk of developing sarcopenia and did not consider primary treatment for that condition. For this reason, exercise that increases muscle strength was not considered as a focus in this section. There is a separate section in the guideline that looked at the role of HRT on the outcome of osteoporosis (see Section 11.6). The group discussed the link between bone strength and reducing fractures and falls for women in menopause.

The group noted that that the extension in women's expected lifespan and increasingly sedentary lifestyles raise a great challenge for the musculoskeletal system…" (NICE HRT 2015) pages 186-192.

In other words,

[(HRT) – (exercise)] = (loss of muscle mass)

[cost of (exercise + HRT)] > (cost of (exercise – HRT)]

2.3.49. In (NICE NG23 2022):

"…Offer menopausal women with, or at high risk of, breast cancer:; information on all available treatment options; information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen; referral to a healthcare professional with expertise in menopause…

(breast cancer) = (no paroxetine and fluoxetine) + (tamoxifen)

… Long-term benefits and risks of hormone replacement therapy…Venous thromboembolism…Explain to women that: the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk; the risk of 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 population risk….Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m2…Consider referring 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.

[high risk of VTE with HRT] > [oral HRT-related risks] > [transdermal HRT-related risks]

…Cardiovascular disease…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….Be aware that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed….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…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 population risk of stroke in women aged under 60 years is very low (see table 2)…

(risk of CHD without HRT) ≥ (risk of CHD with estrogen-only HRT)

(risk of CHD with estrogen-and progesterone-HRT) ≥ (risk of CHD without HRT)

(risk of stroke with oral HRT) ≥ (risk of stroke)

(risk of stroke age < 60) ∈ (negligible)

Contraception

2.3.50. In (NICE HRT 2015):

"…Give information about contraception to women who are in the perimenopausal and postmenopausal phase. See guidance from the Faculty of Sexual & Reproductive Healthcare on contraception for women aged over 40 years…

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

…Explain to women with premature ovarian insufficiency: the importance of starting hormonal treatment either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (unless contraindicated); that the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40; 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 HRT is not a contraceptive…

…The Guideline Development Group considered VTE a critical long-term outcome for evaluating the effect of HRT on women. VTE is associated with long-term morbidity via an increase in pulmonary embolus and is also associated with increased mortality. This complication has been widely reported as being associated with use of sex steroid hormones (such as the combined oral contraceptive pill) which impact the hepatic synthesis of coagulation factors and thus increase the risk of clotting…" and how about oral contraception is a confounding factor in any clinical hormone investigation.

In other words,

[woman] = [(premature menopause) ± (oral contraception) ± (HRT)]

2.3.51. In (NICE NG23 2022):

"…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…

…Give information about contraception to women who are in the perimenopausal and postmenopausal phase. See guidance from the Faculty of Sexual & Reproductive Healthcare on contraception for women aged over 40 years…" and with premature ovarian insufficiency.

(oral contraception) = (no hormone clinical investigation)

Stopping HRT

2.3.52. In (NICE HRT 2015):

under "…Starting and stopping hormone replacement therapy (HRT)…In perimenopausal and postmenopausal women using hormonal replacement therapy (HRT) for vasomotor symptom relief, what is the effectiveness of an abrupt HRT discontinuation strategy compared with a tapered HRT discontinuation strategy?… Four RCTs comparing abrupt discontinuation with tapered discontinuation were included in the review…No prospective cohort studies were found that met this protocol…The quality of the evidence supporting these recommendations was generally of low to very low quality due to the high risk of bias…

…Relative value placed on the outcomes considered…The Guideline Development Group selected the following outcomes as the most important for their decision-making: reoccurrence of menopausal symptoms, which may or may not result in resumption of HRT treatment; uptake of alternative treatment; acceptability of method of discontinuation of HRT treatment by women; the impact on women's HRQoL…

…Consideration of economic benefits and harms…Compared with immediately stopping treatment, a tapering regimen will necessitate the taking of hormone replacement for longer and therefore require a greater treatment cost. However, in the absence of good quality evidence the Guideline Development Group was of the view that a tapered approach could result in a lower recurrence of symptoms in the short term which could potentially reduce other healthcare used to offset the treatment costs and result in a better HRQoL. The group therefore thought that either approach could be offered to women.

…Recommendations…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 the 3-month review appointment, or promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NICE guideline on suspected cancer)…Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment….Explain to women that: gradually reducing HRT may limit recurrence of symptoms in the short term; gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term…" (NICE HRT 2015) pages 127-131.

In other words,

[(cost of tapered withdrawal of HRT) + (risk of short term menopausal symptoms)] ≅ [(cost of sudden withdrawal of HRT) + (risk of long term menopausal symptoms)]

2.3.53. In (NICE NG23 2022):

"…Starting and stopping HRT…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 the 3-month review appointment, or promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NICE guideline on suspected cancer).

…Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment…Explain to women that: gradually reducing HRT may limit recurrence of symptoms in the short term gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term…"

(unexpected vaginal bleeding) ⊂ (endometrial cancer)

(benefit of gradual withdrawal of HRT) > (risk of sudden withdrawal of HRT)

(withdrawal of HRT) = (menopausal symptoms)

Referral to a specialist

2.3.54. In (NICE HRT 2015):

under "…Review and referral… At what intervals should clinical review be undertaken to assess the effectiveness and safety of treatments to relieve menopausal symptoms and to determine when women need to be referred to specialist care?… In the absence of relevant evidence, the Guideline Development Group's recommendations were based on their clinical experience and expert opinion, and on existing guidance…

… If the frequency of clinical review is too great then additional resources will be used for insufficient gain. Conversely, if the frequency is insufficient then the patient may continue on ineffective treatment longer than necessary…

… Recommendations…Discuss with women the importance of keeping up to date with nationally recommended health screening….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).

…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.

…Consider referring women to a healthcare professional with expertise in menopause if: they have menopausal symptoms and contraindications to

HRT or; there is uncertainty about the most suitable treatment options for their menopausal symptoms.

In other words regarding reviews, [cost of reviews] > [(cost of continued treatment) + (menopausal symptoms)]

In other words regarding referral to a specialist, [referral] = [(symptoms of menopause) + (HRT side effects) ± (contraindication to HRT)]

2.3.55. In (NICE NG23 2022), offer referral if breast cancer, consider referral if HRT contraindicated, or high risk of VTE, or premature ovarian insufficiency.

HERE THE NONPROFESSIONAL WOMAN RETURNS FROM (RCOG HRT 2022c) TO (RCOG HRT 2022a) AND THERAFTER DIRECTED TO (NHS HRT 2022a)

2.3.56. The nonprofessional woman is quickly directed from (NHS HRT 2022a) about HRT to (NHS HRT 2022b) about menopause analysed below.

Subsequently:

benefits of HRT are to treat menopausal symptoms (hot flushes, night sweats, mood swings, vaginal dryness, reduced sex drive); HRT offers relief and may prevent osteoporosis;

some types of HRT increase risk of breast cancer

consult with GP to start HRT

HRT may be unsuitable if you've survived cancer and stroke, have hypertension or liver disease, or are pregnant.

types of HRT

increased risk of breast cancer with 2 hormones, risk of breast cancer after HRT withdrawal, tapering recommended

side effects of HRT

alternatives to HRT lifestyle, antidepressents causing dizziness, clonidine, bioidentical hormones link to alternatives to HRT which are lifestyle, tibolone, antidepressants, clonidine, bioidentical hormones, complementary therapies (primrose oil, black cohosh, angelica, ginseng and St John's wort).

Returning to check (NHS HRT 2022b) about menopause:

Age related and premature menopause (premature ovarian insufficiency introduced, followed by symptoms of menopause. Treatment: 2 hormones and various types of HRT, benefts on symptoms and osteoporosis as well as heart disease; no risks mentioned; testosterone; estrogen for vaginal dryness, non-homrone medicine (clonidine, gabapentin, CBT), complementary and alternative therapy (red clover, black cohosh, bioidentical hormones); see also lifestyle changes.

In other words

[menopause – (cancer, stroke, hypertension, liver disease pregnancy)] = HRT.

And in other words (benefits of HRT on symptoms, CVD, osteoporosis) > (HRT-related risk of breast cancer after withdrawal of HRT)

HERE THE NONPROFESSIONAL WOMAN RETURNS FROM (NHS HRT 2022a; 2022b) AND IS DIRECTED TO "…HRT - clinical guideline (NICE)…" WHICH TAKES ONE TO "…Menopos…Tachwedd 2015…Ynglŷn â'r wybodaeth hon…" A DOCUMENT NOT IN ENGLISH CLICK HERE.

NEXT, THE NONPROFESSIONAL WOMAN IS DIRECTED TO Women's Health Concern HRT Factsheet (WHC 2022)

2.3.57. Women's Health Concern HRT factsheet website (*ibid*):

HRT for menopausal symptoms including 'infamous hot flushes!'

types of HRT, local *vs.* systemic HRT explained, former provides very 'local relief'

menstrual cycle changes to expect with types of HRT (1 and 2 hormones)

tibolone

side effects of HRT and tibolone

relief of symptoms using local topical applications

HRT breast cancer and heart disease, user directed to NHS website on HRT benefits and risks (importantly clinical review once per year)

user is directed to NHS website on Complementary/alternative therapies for menopausal women (CBT, herbal, black cohosh, St John's wort, isflavones soya red clover, acupuncture, SSRIs, gabapentin, clonidine, "…This guidance is evidence based, not individualised and it is possible you might be one of the two percent who responds extremely well to one or more of these alternatives…", breast cancer survivor advice, importance of individualized treatment.

2.3.58. Other data of interest in (NICE HRT 2015)

"…Use of absolute effect in decision-making: The Guideline Development Group assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio with the exception of estimation of baseline risk for breast cancer and cardiovascular disease (CVD).

For CVD there were a number of outcomes of interest for which it was necessary to estimate baseline incidences. Chronic heart disease (CHD) incidence was obtained from a UK study by Weiner (2008) which reported the rate in person-years of myocardial infarction (MI) in women younger

than 55 years and older than 55 years separately. A weighted average of these rates was calculated and this was multiplied by the average length of included studies follow-up to give an incidence of CHD of 15 per 1000 people over 7.5 years. No information was found for the baseline incidence for the outcome of CHD death. Therefore the incidence of CHD death and CHD were assumed to be equivalent, though results should be interpreted with caution due to unavailability of accurate baseline information for this outcome.

The rate of stroke was taken from the same UK study (Weiner 2008) and the incidence was calculated in the same way. The baseline incidence of stroke was 11.3 per 1000 women over 7.5 years. As the majority of strokes are ischaemic, the baseline incidence of ischaemic stroke was assumed to be the same. However, as haemorrhagic strokes are rarer and UK data were not available for this outcome, we used the incidence in the control arm from any study reporting haemorrhagic stroke as the baseline risk.

As a composite of both MI and stroke, the incidence of CVD in untreated women was estimated to be the incidence of both stroke and MI, obtained by adding the rates from the Weiner (2008) study. This gave a baseline incidence of 26.3 per 1000 women over 7.5 years. The incidence of CVD death was considered to be equal to CVD.

As reliable UK data was not available for the incidence of fragility fractures, the incidence of CHD or CHD death in women with pre-existing heart disease, we used the incidence in the control arms from studies reporting this outcome in this population (default GRADE approach). The absolute risk therefore reflected the duration of the study or studies that contributed to these results and more information is provided as footnotes in the relevant tables…" (NICE HRT 2015) page 43.

"…Data synthesis using network meta-analysis

A network meta-analysis (NMA) was formulated to synthesise direct and indirect evidence of treatments' efficacy to relieve short-term menopausal symptoms while preserving randomisation for the outcomes of frequency of vasomotor symptoms (VMS), discontinuation of treatment and vaginal bleeding. Hierarchical Bayesian NMAs with class effects were performed using the software WinBUGS version 1.4. Data from women in 3 distinct populations were used as inputs to the models: women with a uterus, women without a uterus and women with breast cancer or a history of breast cancer. We examined statistical models for fixed and random effects that allowed inclusion of multi-arm trials and accounted for the correlation between arms in the trials with any number of trial arms. These models were based on original work from the University of Bristol (https://www.bris.ac.uk/cobm/research/mpes/mtc.html).

As no dependency on time was identified, discontinuation of treatment and vaginal bleeding were treated as dichotomous outcomes and were modelled on the log-odds ratio scale. Frequency of VMS was distributed in the form of an overdispersed Poisson distribution and was therefore modelled on the log-mean ratio scale. On this scale, final and change from baseline

frequencies of VMS could not be pooled, so a correlation coefficient was used to estimate final frequencies from change from baseline.

For all the networks set up in the NMA, models for fixed and random effects were developed and then these were compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. However, if the difference in DIC between a fixed and random effects model was less than

5 points, and the models make very similar inferences, then we would report the results from a fixed effects model as it does not make as many assumptions as the random effects model, contains fewer parameters and is easier for clinical interpretation than the random effects model.

Where closed loops of treatment comparisons existed in the networks, inconsistency was assessed by comparing any available direct and indirect treatment and testing the null hypothesis that the indirect evidence was no different from the direct evidence.

There were 3 main outputs from the NMA: the estimation of summary estimates (means ratios [MRs] or odds ratios [ORs]) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence; the probability that each treatment was best based on the proportion of Markov chain iterations in which treatment had the highest probability of achieving the outcomes selected in the networks; the ranking of treatments compared with baseline groups (presented as median rank and its 95% credible intervals).

The following sensitivity analyses were conducted: changes to the value of the correlation coefficient used to estimate final frequencies of VMS from change from baseline: combining women with and without a uterus into a single population to determine if this led to changes in heterogeneity; removing low dose oral oestradiol plus progestogen to determine if this dose was reducing the overall efficacy of oral oestradiol plus progestogen in the model.

…Type of studies…Randomised controlled trials (RCTs), non-randomised trials and observational studies (including diagnostic or comparative cohorts) were included in the evidence reviews as appropriate…

…Appraising the quality of evidence by outcomes…The evidence for outcomes from the included RCTs and, where appropriate, observational studies was evaluated and presented using an adaptation of the GRADE toolbox developed by the international GRADE working group. The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled

outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of randomized or completers) for binary outcomes. Reporting of publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the Guideline Development Group. However, given the nature of most of the review questions included in this guideline (driven by short- or long-term outcomes), the categorisation of outcomes as critical and important did not follow the standard GRADE approach. The outcomes selected for a review question were critical for decision-making in a specific context.

The evidence for each outcome in interventional reviews was examined separately for the quality elements listed and defined in Table 4. Each element was graded using the quality levels listed in Table 5." (NICE HRT 2015) pages 36-38.

3. Summary of data analysis

3.1. Equations describing data underpinning what the nonprofessional woman sees in order of appearance to her

Data entry nonprofessional woman sees in italics. Data in (NICE HRT 2015) is unshaded.

Data in (NICE NG23 2015) is shaded grey.

Menopause as reduced hormones requiring topping up

$$HRT = [(age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)]$$

Hot flushes and night sweats or vasomotor symptoms

$$(menopausal\ symptoms) = (woman) - (HRT)$$

$$(menopausal\ symptoms) = (frequency\ hot\ flush) + (anxiety\ low\ mood) + (frequency\ sexual\ intercourse) + (muscle\ pain)$$

$$(outcome\ of\ menopausal\ symptoms) = (vaginal\ bleeding) + (discontinuation\ of\ treatment)$$

$$(woman's\ baseline\ characteristics) \notin (menopausal\ symptoms)$$

$$[benefit\ of\ HRT] > [cost\ of\ (risks\ of\ HRT)]$$

$$(anxiety\ low\ mood) = (anxiety\ low\ mood) - (depression)$$

$$(depression) = (low\ mood)$$

$$(low\ mood) = 0$$

$$(diagnosis) = (information\ to\ woman)$$

$$(diagnosis) = (information\ to\ woman)$$

$$HRT = [(age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)]$$

Vaginal dryness

$$(menopausal\ symptom) = (woman) - (HRT)$$

$$(menopausal\ symptom) \subset \{urogenital\ atrophy\}$$

$$HRT = (systemic\ HRT) + (local\ topical\ hormone\ application)$$

$$(vaginal\ dryness) = (urogenital\ atrophy)$$

Sex drive, desire, or libido

$$(libido) = [(frequency\ sexual\ intercourse) - (urogenital\ atrophy\ vaginal\ dryness) - (anxiety\ painful\ intercourse)]$$

$$[benefit\ of\ (high\ frequency\ sexual\ intercourse)] \geq [cost\ of\ (urogenital\ atrophy\ vaginal\ dryness) + (anxiety\ painful\ intercourse)]$$

$$(low\ libido) = (HRT) + (testosterone)$$

$$(low\ libido) = (HRT) + (testosterone)$$

Stress incontinence or leaking urine

$$(menopausal\ symptom) = (woman) - (HRT)$$

$$(menopausal\ symptom) \subset \{urinary\ incontinence\}$$

$$(menopausal\ symptom) \in (urogenital\ atrophy)$$

Bone thinning leading to osteoporosis and fractures

$$(menopausal\ symptom) \subset \{osteoporosis\}$$

$$(osteoporosis) = (fractures)$$

$$[cost\ of\ (exercise + HRT)] > [cost\ of\ (exercise - HRT)]$$

$$(premature\ menopause) \in (menopausal\ symptoms)$$

$$(menopausal\ symptom_m) \in (osteoporosis)$$

$$(menopausal\ symptom_m) \in (sarcopenia)$$

$$(osteoporosis) = (fractures)$$

$$(HRT) \pm (oral\ contraception) = (decreased\ risk\ of\ osteoporosis\ and\ CVD)$$

$$[cost\ of\ informing\ women\ about\ exercise] > [benefit\ of\ exercise\ on\ osteoporosis]$$

Anxiety and low mood

$$(anxiety\ low\ mood) = (anxiety\ low\ mood) - (depression)$$

$$(depression) = (low\ mood)$$

$$(low\ mood) = 0$$

$$[(anxiety\ low\ mood) + (menopausal\ symptoms)] = [(HRT) \pm (CBT)]$$

$$[(menopausal\ symptoms) - (depression)] = [(HRT) - (SSRIs)]$$

$$[(anxiety\ low\ mood) + (menopausal\ symptoms)] = [(HRT) \pm (CBT)]$$

$$(anxiety\ low\ mood) \in (menopausal\ symptoms)$$

$$(anxiety\ low\ mood) \in (libido)$$

$$(menopausal\ symptom_a) \in (depression)$$

No hormone test required before diagnosis of menopause

$$(premature\ menopause) = [(age \geq 40) \pm (uterus) + (menopausal\ symptoms) + (2\ FSH\ samples)]$$

$$(premature\ menopause) = [(age \geq 40) \pm (uterus) + (menopausal\ symptoms) + (2\ FSH\ samples)]$$

Lifestyle changes

$$(lifestyle\ changes) \notin (HRT)$$

$$(obesity) \subset \{lifestyle\ changes\}$$

St John's wort

$$(breast\ cancer) = (no\ St\ John's\ wort)$$

Black cohosh

$$(black\ cohosh) \notin (HRT)$$

$$[(risk\ of\ black\ cohosh) + (cost\ of\ standardising\ black\ cohosh)] > [(cost\ of\ HRT) + (benefit\ of\ HRT)]$$

$$[risk\ of\ black\ cohosh\ and\ isoflavones] > [benefit\ of\ black\ cohosh\ and\ isoflavones]$$

Isoflavones, acutherapy, homeotherapy, aromatherapy, bioidentical hormones, clonidine, gabapentin, CBT

$$(isoflavones, acutherapy, homeotherapy, aromatherapy, bioidentical\ hormones, clonidine, gabapentin, CBT) \notin (HRT)$$

Testosterone

$$(testosterone) = (increased\ frequency\ sexual\ intercourse)$$

$$HRT = (estrogen) \pm (progesterone) \pm (testosterone)$$

$$[(low\ libido) + (HRT\ without\ testosterone)] = (HRT\ with\ testosterone)$$

Long-term risks and benefits of HRT

$$[(high\ risk\ of\ VTE\ with\ HRT) + (low\ risk\ of\ DVT\ and\ PE)] > [risk\ with\ oral\ HRT] > [risk\ with\ transdermal\ HRT]$$

$$[absolute\ risk\ of\ CVD\ with\ HRT] > [relative\ risk\ of\ CVD\ with\ HRT] \geq [risk\ of\ stroke\ with\ HRT] > \left[(risk\ of\ CVD\ with\ oral\ HRT) > [risk\ of\ CVD\ with\ transdermal\ HRT]\right]$$

$$(HRT\ withdrawal) = (increased\ risk\ of\ T2DM)$$

$$(measuring\ fasting\ blood\ glucose\ and\ HbA1c) = (improved\ outcome\ for\ women\ on\ HRT)$$

$$[cost\ of\ measuring\ blood\ glucose] > [(cost\ of\ HRT_{related}T2DM) + (risk\ of\ HRT_{related}T2DM)]$$

$$[risk\ of\ HRT_{related}breast\ cancer] < [cost\ of\ HRT_{related}breast\ cancer]$$

$$(dementia) \notin (HRT_{related}life$$

$$[(HRT) - (exercise)] = (loss\ of\ muscle\ mass)$$

$$[cost\ of\ (exercise + HRT)] > [cost\ of\ (exercise - HRT)]$$

$$[high\ risk\ of\ VTE\ with\ HRT] > [oral\ HRT_{related}risks] > [transdermal\ HRT_{related}risks]$$

$$[risk\ of\ CHD\ without\ HRT] \geq \left[risk\ of\ CHD\ with\ HRT_{estrogen}\right]$$

$$\left[risk\ of\ CHD\ with\ (HRT_{estrogen} + HRT_{progesterone})\right] \geq [risk\ of\ CHD\ without\ HRT]$$

$$[risk\ of\ stroke\ with\ oral\ HRT] \geq [risk\ of\ stroke]$$

$$(risk\ of\ stroke\ age < 60 \in (negligible)$$

Contraception

$$[woman] = [(premature\ menopause) \pm (oral\ contraception) \pm (HRT)]$$

$$(oral\ contraception) = (no\ hormonal\ investigation)$$

Stopping HRT

$$[(cost\ of\ tapered\ withdrawal\ of\ HRT) + (risk\ of\ short\_term\ menopausal\ symptoms)]$$
$$\cong [(cost\ of\ sudden\ withdrawal\ of\ HRT) + (risk\ of\ long\_term\ menopausal\ symptoms]$$

$$(unexpected\ vaginal\ bleeding) \subset (endometrial\ cancer)$$

$$[benefit\ of\ tapered\ withdrawal\ of\ HRT] > [risk\ of\ sudden\ withdrawal\ of\ HRT]$$

$$(withdrawal\ of\ HRT) = (menopausal\ symptoms)$$

Referral

$$[cost\ of\ reviews] > [cost\ of\ (continued\ HRT) + (menopausal\ symptoms)]$$

$$(referral) = [(symptoms\ of\ menopause) + (HRT\ side\ effects) \pm (contraindication\ to\ HRT)]$$

3.2. Comment on equations describing data in (NICE HRT 2015) and (NICE NG23 2015)

Guideline developers based their HRT recommendations on three hierarchies of evidence:

(i) Clinical trials whether deemed randomized or not or (R)CTs. Data from these was often put in an 'NMA', a 'network meta-analysis';

(ii) Cohorts. Data from these was looked at one by one and may have been used in other ways;

(iii) The experience of the developers.

The Guideline developers process data in units. For example, data indicating symptoms of menopause were defined in (NICE HRT 2015) as:

- vasomotor symptoms or hot flushes and night sweats. The effect of treatment on vasomotor symptoms is measured using frequency of hot flushes and not severity of hot flushes nor night sweats. This outcome (effect of treatment *vs.* placebo on frequency of hot flushes) is measured on the short-term and the long-term, five and ten years.
- Sex drive or libido, this is measured by frequency of sexual intercourse and other indicators.
- anxiety and low mood are vaguely measured without depression.
- muscle and joint ache and pain.

It is important to note that this is a data definition of menopausal symptoms in (NICE HRT 2015), the 'full guideline, methods, evidence, and recommendations'. For the present, the user is unknown. Data definitions of menopausal symptoms in the (NICE NG23 2015) guideline for the health professional, or the websites for the nonprofessional woman (RCOG HRT 2022b; 2022c), may vary – if present.

Data used by developers of the guidelines is processed in units. It is not possible to call these units 'nodes' nor 'operators' because they do not work like that across guidelines. From a physiological perspective (which is to say, sociological), these units are 'creatures': bits of discrete information which react with other bits of information to produce new, combined information.

In this way, menopausal symptoms data are (frequency of hot flushes) + (anxiety and low mood) + (frequency of sexual intercourse) + (aches in joints and muscles) creatures.

At this stage one may find this problematic. For example, (frequency of sexual intercourse) is not, from a physiological perspective, quite the same as (sex drive or libido), another creature in the guidelines. These disagreements regarding frequency of putative orgasms are set aside now. Similarly, the creature of (anxiety and low mood) will not be questioned from any depth psychology perspective, and simply allowed to be, and to combine with other creatures potentially in the whole world of guidelines.

Data used by guideline developers is processed in units or creatures. These were vital to place into the network meta-analysis. We can think of it as a huge machine that combines creatures in the most divine way, to tell us about all the other creatures it is connected to. Most of the time the network meta-analysis was fed data of moderate or low quality (high risk of bias). And much of the time the network meta-analysis said no. Maybe there were not enough participants in the (R)CTs data, or there were but the studies were mostly biased. Maybe (severity of hot flushes) was a poisonous creature and had to be banished from this network meta-analysis – not the entire world of guidelines and other network analyses.

It appears (vasomotor symptoms) was too amorphous a creature, and so was disassembled to (frequency of hot flushes), (severity of hot flushes), and (night sweats). And then (severity of hot flushes) was subdued, and (frequency of hot flushes) became of importance to menopausal symptoms. This is certain because (frequency of hot flushes) ended up defining menopausal symptoms data, along with others which can be assigned a value of zero (0, null, nil). I did not put brackets around menopausal symptoms so it is not a creature yet.

So we have disassembled (vasomotor symptoms) and subdued (severity of hot flushes), but maybe the network meta-analysis still says no. Maybe, we cannot tell for sure because its ways are effectively mysterious, the network meta-analysis, like studies from women have shown, just cannot tell you for sure that (severity of hot flushes) and (night sweats) have any significant relationship affecting yet a third creature in the network, or more. It's complicated, the relationships. Ok?

The guideline developers may then soothe the network meta-analysis in question. For example, the developers may tell the network meta-analysis not to be concerned about the relationship between (breast cancer) creatures and (ever was, or is on, HRT) creatures. There may not be enough data inside those creatures in the network, let alone (breast cancer currently on HRT), (breast cancer was on HRT last 5 years), (breast cancer never HRT), and many other variations of those creatures (time of cancer, type, stage, so on). So pretend it's just (breast cancer never on HRT) regardless of fact for this network-metanalysis, and feed some more numbers, women, not participants in (R)CTs, there you go. With this massage, maybe the network meta-analysis will stop saying no and tell us something.

While all hail the network meta-analysis, it is important to note that the creatures exist outside the network meta-analysis, namely in cohort studies and the developers' experience. The creatures then engage with reality through the guideline for healthcare professionals, and websites for nonprofessional women.

These creatures are, to the best of my understanding, chimeras of data *and* language. In the process of moving from (NICE HRT 2015) guideline, to the guideline for healthcare professionals (NICE NG23 2015), to the guideline for the nonprofessional woman on websites (RCOG HRT 2022b; 2022c), the creatures are cartoonified.

The data units or creatures, which are language /written symbols which may have sounds used in society to tell stories and make decisions/, *and* data /for example, numbers of women over 45 reporting bothersome menopausal symptoms not presently suffering diabetes and hypertension assumed never to have had breast cancer without a uterus who responded to locally and/or systemically administered HRT one-or-two hormone oral contraception status unresolved over 5 years with significantly less frequent hot flushes/, are used to process information. The output of this information processing is other information which includes decisions on *what to put in the guidelines for healthcare professionals and nonprofessional women*. It also includes decisions on which creatures we need more of or need more data inside them, research recommendations.

Returning to the example of menopausal symptoms:

$$(short\_term\ effect\ of\ treatment \text{ vs. } placebo\ on) = (frequency\ hot\ flush) + (anxiety\ low\ mood) + (frequency\ sexual\ intercourse) + (muscle\ pain)$$

As seen from the equation, it is not quite menopausal symptoms. The data, the creatures of 'menopausal symptoms' are in fact 'the effect of treatment *vs.* no treatment on menopausal symptom(s) of interest in a 5 year range'. (short-term effect of treatment on a or the menopausal symptom(s) *vs.* none 5 year) is awkward, so (menopausal symptoms) will be used, where (menopausal symptoms) = (short-term effect of treatment or none on the creatures of (frequency hot flush), (frequency of sexual intercourse), (anxiety low mood), and (muscle pain)):

$$(menopause\ symptoms) = (frequency\ hot\ flush) + (anxiety\ low\ mood) + (frequency\ sexual\ intercourse) + (muscle\ pain)$$

Because (menopause symptoms) is an *effect of treatment*, it has an outcome. One may assume that 'decreased frequency of hot flushes' is an outcome of 'treatment using an active agent' – incorrectly. The developers had reasons for not defining (outcome of menopause symptoms) the same as (menopause symptoms) or the effect of short-term treatment on menopause symptoms *vs.* placebo, see paragraph 2.3.8.

$$(outcome\ of\ menopause\ symptoms) = (vaginal\ bleeding) + (discontinuation\ of\ treatment)$$

But (outcome of menopause symptoms) is not composed of the same creatures as (menopause symptoms)? Obviously not. The creatures are related. We depend on the developers of the guidelines to discuss and come to a decision on what to recommend, and what to put in the guidelines. Perhaps after a session or two with the relevant network meta-analysis.

In the present example, this information is: (i) a recommendation on how to diagnose and mange menopausal symptoms; and (ii) information given in

guidelines to known users. In other words, some kind of 'diagnosis' creature and some kind of 'information to the patient' creature.

$$(menopause\ symptoms) = (frequency\ hot\ flush) + (anxiety\ low\ mood) + (frequency\ sexual\ intercourse) + (muscle\ pain)$$

…where (menopause symptoms) is short-term effect of a treatment on a menopausal symptom, and the outcome can be (vaginal bleeding) and/or (discontinuation of treatment).

Let's look at the (frequency sexual intercourse) creature. This creature, as we may recall, came out of a creature called sex drive or (libido). This (libido) creature is related to the (frequency sexual intercourse) creature in the guidelines in the following manner:

$$libido = (frequency\ sexual\ intercourse) + (urogenital\ atrophy) + (anxiety)$$[13]

For this reason, it was not necessary, for example, to include 'vaginal dryness' *per* se in data processed by the network for the purpose of finding out what the short-term effects of a treatment *vs.* placebo is on vaginal dryness. Because:

$$(menopausal\ symptom_f) \subset \{urogenital\ atrophy\}$$

…where, in this instance, the (menopausal symptom) of (vaginal dryness) is a subset of another creature completely, with its own set of data and guidelines for the unknown user. The reader is requested to withhold judgement on use of $\subset$(A *is a subset of* B)…as opposed to $\in$(A *is an element* of B).

The RCOG websites on HRT for the nonprofessional woman did not discuss local vaginal hormone products, or hormone-containing products applied directly to the vagina and which do not artificially raise serum hormone levels, see paragraph 2.1. The WHC websites did, see paragraph 2.3.56. This is because, in the NICE guideline for the unknown user:

$$HRT = (systemic\ HRT) + (local\ hormone\ application)$$

…where (local hormone application) does not artificially raise serum hormone levels and (systemic HRT) does.

Indeed, we find that in (NICE NG23 2015) and websites for the nonprofessional women, HRT is assumed to be any product containing hormones, regardless of route of administration, and regardless of whether or not a dose of the product raises serum hormone levels. Again, (local hormone application) may equal zero (0, nil, null).

[13] Two negatives make a positive if (urogenital atrophy) carries a negative valence and is subtracted from (frequency sexual intercourse). The same for (anxiety).

Returning to the vasomotor symptoms of menopause, hot flushes and night sweats. Recall that (menopausal symptoms) is, in data terms, a creature derived from several 'the short-term effect of treatment *vs.* placebo on a menopausal symptom' creatures. The developers found that (HRT) and (black cohosh) may have a beneficial relationship with a creature related to (menopausal symptoms), namely (vasomotor symptoms): featuring (frequency of hot flushes), and side roles for (severity of hot flushes) and (night sweats). There were lots of buts: 'but the data is bad…but we do not have enough data', and those massage and feeding sessions with the network meta-analysis, but never mind all that now. Those putatively beneficial effects of HRT and black cohosh were judged by (outcome of menopausal symptoms), which is (vaginal bleeding) and (discontinuation of treatment).

The vasomotor symptoms of menopause are important for diagnosing menopause. But according to the data in (NICE HRT 2015) for unknown user:

$$(diagnosis) = (information\ to\ the\ patient)$$

We are after a 'diagnosis of menopausal symptoms' which should include a 'vasomotor symptoms' creature of some kind. It is derived from a one-to-one interpretation of the guideline's data for diagnosis of menopause *which is not the same thing as (diagnosis)*. The recommendation on how to diagnose menopause or (diagnosis) is not the same creature as (menopausal symptoms). They are related.

$$HRT = (age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)$$

This is well reflected in information given to known users. What a woman sees when she logs onto the RCOG websites on HRT and 'treatment of menopause' (RCOG HRT 2022a/b/c) is that menopause is an age-related reduction in the body's endogenous hormones, and which needs to be topped up. There are some 'buts' which come later, but do you have a uterus, diabetes, or hypertension, but if survived breast cancer, but there might be risks, but it might be good for your bones. In general, the nonprofessional woman is reassured that the health system can address those buts, just talk to someone and you will be sorted out. If you are over 45 and have symptoms of menopause, you will be offered HRT.

The age required for a woman to fit into (HRT) is 40 and above. This is because what the woman and health care professional see is a mish mash of data about menopause and 'premature ovarian insuffiency'. So for the purpose of processing data, combining creatures in a network, it is not necessary to immediately distinguish between a woman who is over 45 and going through menopause, and a woman who is still around 40 and might have fewer gamete-producing cells than what we expect. She might even have a distinct inheritable condition, any one of the *pathological* causes of secondary amenorrhea. A woman with 'premature ovarian insufficiency', or any kind of premature menopause, will be identified later, as the (premature menopause) creature, and which follows a slightly different path *after*:

$$HRT = (age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)$$

The path (premature menopause) will take is:

$$(premature\ menopause) = [(age \geq 40) \pm (uterus)] + (menopausal\ symptoms) + (2\ elevated\ FSH\ samples\ 2\ to\ 6\ weeks\ apart)$$

…and which is derived from data in (NICE HRT 2015) reflecting the datum 'no hormone tests required before HRT' shown on the RCOG website to nonprofessional women see paragraph 2.3.29.

For this reason, the age of the woman in the equation:

$$HRT = (age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)$$

…is ≥ 40 and not 45.

For all of 'hot flushes and night sweating', 'vaginal dryness', and 'stress incontinence', which the nonprofessional woman sees on the RCOG websites, relevant data in (NICE HRT 2015) gives the following equation among others:

$$(menopausal\ symptoms) = (woman) - (HRT)$$

And so it becomes clear why the healthcare professional and nonprofessional woman are told about bothersome menopausal symptoms, premature ovarian insufficiency, and HRT in the same breath.

This also explains why menopausal symptoms are listed in (NICE NG23 2015) for the healthcare information under 'information to the patient' see paragraph 2.3.11:

$$(diagnosis) = (information\ to\ patient)$$

This is an example of where the same equation is in both (NICE HRT 2015) and (NICE NG23 2015). The equation describing data in (NICE NG23 2015) for healthcare professionals may more meaningfully read:

$$(information\ to\ patient) = (diagnosis)$$

…and from a mathematical perspective such a distinction can be disregarded of course.

To distinguish between equations and phrases in (NICE HRT 2015) for unknown user, and equations and phrases in (NICE NG23 2015) for healthcare professionals, the latter will be shaded grey. So in (NICE HRT 2015) for unknown user:

$$(diagnosis) = (information\ to\ patient)$$

…and in (NICE NG23 2015) for healthcare professional:

$$(diagnosis) = (information\ to\ patient)$$

Data in (NICE HRT 2015) used to generate the menopausal symptoms on the websites for nonprofessional women is given by:

$$HRT = (age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)$$

Data in (NICE NG23 2015) used to generate the diagnosis, the most comprehensive list of symptoms in that guideline for healthcare professionals see paragraph 2.3.11., is described by:

$$HRT = (age \geq 40 + vasomotor\ symptoms) \pm (uterus) \pm (oral\ contraception)$$

The former has a (menopausal symptoms) creature, the latter a (vasomotor symptoms) creature. Data in (NICE NG23 2015) describing the symptoms of menopause is not the whole set of data describing the symptoms of menopause in (NICE HRT 2015). In (NICE HRT 2015), (vasomotor symptoms) is made up of (frequency hot flush), (severity hot flush), and (night sweat). The lattermost two are downplayed, and (frequency hot flush) is the dominating creature inside (vasomotor symptoms). This creature (vasomotor symptoms) is actually 'short-term benefit of HRT *vs.* none on frequency of hot flushes where discontinuation of HRT is an adverse outcome', data-wise.

The point here is to see that creatures change from one guideline to the other. In the example discussed just above, the reasoning behind the change of (menopausal symptom) to (vasomotor symptom) from one guideline to the other is congruent, is supported by data. The developers explain in (NICE HRT 2015) why (vasomotor symptoms) is important for (menopausal symptoms), why (frequency hot flush) was chosen over (severity hot flush) and (night sweat). And this is reflected in (NICE NG23 2015) data concerning menopausal symptoms told to the patient by healthcare professional in that (vasomotor symptoms) is key. The creatures change, their stuffing is very different, but they are related. It gets dumbed down, and at the same time it confirms what is important.

Recall that

$$(menopausal\ symptom_f) \subset \{urogenital\ atrophy\}$$

…where menopausal symptoms of (frequency of sexual intercourse) and (vaginal dryness) are processed in a network not presently of direct interest, or a separate set of guidelines.

Similarly for 'leaking urine' which the woman sees on the websites. The data in (NICE HRT 2015) related to 'leaking urine' produces:

$$(menstrual\ symptom_u) \subset \{urinary\ incontinence\}$$

These urinary/menopausal symptoms need to be resolved for the healthcare professional user of the clinical guideline NICE NG23:

$$(vaginal\ dryness) = (urogenital\ atrophy)$$

…and

$$(menopausal\ symptom) \in (urogenital\ atrophy)$$

The healthcare professional may consider and offer a treatment for a menopausal symptom which is an element of urogenital atrophy in the healthcare professional guideline (NICE NG23 2015). The healthcare professional may also pull up the guideline on urogenital atrophy, which state-of-the-art RCOG recommendation appears to treat as atrophy in the literal sense, by some form of cautery. But there are things to try out first *within* (NICE NG23 2015) for vaginal dryness, painful intercourse, and urinary symptoms of menopause. The healthcare professional needs only to consider a discrete subset of recommendations – (urogenital atrophy) under (HRT) in the (NICE NG23 2015), and not the entire database of {urogenital atrophy} for unknown user. For this reason, $\subset$ as well as $\in$ are used in (NICE HRT 2015) as appropriate, and $\in$ only is used in NICE NG23 for health professionals with one exception.

In this way, {urogenital atrophy} and {urinary incontinence} translocated quite a few menopausal symptom creatures out of the (NICE HRT 2015) data. A 'stress or urine incontinence' creature of some kind has no direct relation to (menopausal symptoms) in the network. (vaginal dryness) and (painful intercourse) are subsumed into (urogenital atrophy) in the definition of (libido), which is not to say {urogenital atrophy}, another network and kettle of fish.

Another example of 'dumbing down' and 'highlighting what is important' when moving from (NICE HRT 2015) to (NICE NG23 2015) is the menopausal symptoms associated with muscle and joint aches and pains. In (NICE HRT 2015), only two equations are necessary to describe the creatures of these symptoms. The data in (NICE HRT 2015) describing the datum of 'muscle pain' which the nonprofessional woman sees is given by:

$$(menopausal\ symptom_m) \subset \{osteoporosis\}$$

…where (menopausal symptom_m) here is a group of muscle and bony symptom related creatures, and:

$$(osteoporosis) = (fractures)$$

…as in bony fractures.

In other words, the data in (NICE HRT 2015) used to generate all recommendations for all users regarding osteoporosis is data concerning fractures. Osteoporosis was indicated by, or defined as fractures in menopausal women of some kind. From a data perspective, osteoporosis and fractures are identical.

In (NICE NG23 2015) for healthcare professionals, another qualification is required for the menopausal symptom of muscle and joint pain and ache:

$$(menopausal\ symptom_m) \in (sarcopenia)$$

…where sarcopenia is some kind of muscle and joint wasting.

The data regarding muscles and not fractures in (NICE HRT 2015) produces the following:

$$[(HRT) - (exercise)] = (sarcopenia)$$
$$[cost\ of (exercise + HRT)] > [cost\ of\ (exercise - HRT)]$$
$$(sarcopenia) = 0$$

In other words there is no data whatsoever inside (sarcopenia) in (NICE HRT 2015).

And in the (NICE NG23 2015) for healthcare professionals we find that:

$$(osteoporosis) = (fractures)$$

$$(sarcopenia) \in (menopausal\ symptoms)$$

…and indeed there is no mention whatsoever of 'exercise' in (NICE NG23 2015) for healthcare professionals. One may not wonder why, since the developers know for sure, from the network meta-analysis and cohort studies as well as experience, that HRT without exercise is associated with muscle wasting – arguably the definition of sarcopenia is HRT without exercise – since the cost of opening that can of worms is greater than the cost of just HRT.

By tracing an entry of *what appears to the woman,* to the data in (NICE HRT 2015) used to produce that entry, one works one way through almost the entire (NICE HRT 2015) data, including appendices – everything except (information to the patient). This creature is not of physiological nature, it has no clinical relevance where 'clinical' is history, examination, and investigations such as lab. The creature (information to the patient) *appears in the clinic* as:

$$(diagnosis) = (information\ to\ patient)$$

…for unknown user of (NICE HRT 2015), and:

$$(information\ to\ patient) = (diagnosis)$$

…for healthcare professional users of (NICE NG23 2015).


DATA WOMAN SEES
DATA UNKNOWN USER SEES
DATA HEALTHCARE PROFESSIONAL SEES
Menopause as illness
Hot flushes and night sweats
Vaginal dryness
Sex drive desire libido
Leaking urine
Bone thinning
Anxiety low mood
No hormone test
Lifestyle
St John's
Black cohosh
Isoflavones
Acutherapy
Homeotherapy
Bioidentical hormones
Clonidine
Gabapentin
CBT
Testosterone
Long-term risks and benefits
Contraception
Stopping HRT
Referral
[woman] = [(premature menopause) ± (oral contraception) ± (HRT)]
(premature menopause) = [(age ≥ 40) ± (uterus) + (menopausal symptoms) + (2 FSH samples)]
(menopausal symptoms) = (woman) − (HRT)
HRT = [(age ≥ 40) ± (menopausal symptoms) ± (uterus) ± (oral contraception)]
(woman's baseline characteristics) ∉ (menopausal symptoms)
HRT = (systemic HRT) + (local topical hormone application)
(menopausal symptom_f) ⊂ {urogenital atrophy}
(menopausal symptom_u) ⊂ {urinary incontinence}
(menopausal symptom_os) ⊂ {osteoporosis}
(lifestyle changes) ∉ (HRT)
(obesity) ⊂ {lifestyle changes}
(alternative therapies) ∉ (HRT)
[(high risk of VTE with HRT) + (low risk of DVT and PE)] > [risk with oral HRT] > [risk with transdermal HRT]
[absolute risk of CVD with HRT] > [relative risk of CVD with HRT] ≥ [risk of stroke with HRT] > [(risk of CVD with oral HRT) > [risk of CVD with transdermal HRT]]
(HRT withdrawal) = (increased risk of T2DM)
[risk of HRT_related breast cancer] < [cost of HRT_related breast cancer]
[(HRT) − (exercise)] = (loss of muscle mass)
(premature menopause) ∈ (menopausal symptoms)
(diagnosis) = (information to woman)
(vaginal dryness) = (urogenital atrophy)
(oral contraception) = (no hormonal investigation)
(breast cancer) = (no St John's wort)
[risk of black cohosh and isoflavones] > [benefit of black cohosh and isoflavones]
(low libido) = (HRT) + (testosterone)
[risk of stroke with oral HRT] ≥ [risk of stroke]
[risk of CHD with (HRT_estrogen + HRT_progesterone)] ≥ [risk of CHD without HRT]
[risk of CHD without HRT] ≥ [risk of CHD with HRT_estrogen]
(risk of stroke age < 60 ∈ (negligible)
[high risk of VTE with HRT] > [oral HRT_related risks] > [transdermal HRT_related risks]
(HRT) ± (oral contraception) = (decreased risk of osteoporosis and CVD)
(withdrawal of HRT) = (menopausal symptoms)
(unexpected vaginal bleeding) ⊂ (endometrial cancer)

Figure 1.

4. What the woman see

The first thing the nonprofessional woman see when she logs onto RCOG and NHS websites about menopause and treatments for its symptoms is hormone replacement therapy or HRT. Menopause is explained as a decrease in endogenous estrogen, and which needs to be 'topped up' with HRT. That menopause is caused by reduction of hormones which causes disease is false for reasons mentioned in paragraphs 2.3.3 and 2.3.4. Briefly, hormone dynamics in menopausal women are unknown, and menopause confers fitness on hominid societies including modern.

The equation describing the (woman) creature in (NICE HRT 2015) is given by data in the guideline related to the *contraception* datum entry which the woman sees on RCOG websites:

$$[woman] = [(premature\ menopause) \pm (oral\ contraception) \pm (HRT)]$$

And since menopausal symptoms are merely:

$$(menopausal\ symptoms) = (woman) - (HRT)$$

…it becomes natural that menopause is a disease caused by absence of HRT.

From a physiological perspective, these definitions raise two concerns: (i) is premature menopause or any other pathophysiological cause of secondary amenorrhea subsumed under psychosomatic menopausal experiences?; and (ii) how is premature menopause differentiated from menopause in reality? The answer to the first question is: Yes, for the purpose of developing guidelines, data woman's age ≥ 45 is not a necessary feature of the (woman) creature. Indeed, in (NICE NG23 2015), we find that:

$$(premature\ menopause) \in (menopausal\ symptoms)$$

…confirming that the healthcare professional need not be concerned with age of presentation, provided the answer to the second question:

$$(premature\ menopause) = [(age \geq 40) \pm (uterus) + (menopausal\ symptoms) + (2\ FSH\ samples)]$$

…keeping in mind that:

$$(oral\ contraception) = (no\ hormonal\ investigation)$$

Importantly, no evidence exists in (NICE HRT 2015) that menopause is caused by a reduction in hormone levels which require topping up. This was not necessary because:

$$HRT = [(age \geq 40 + menopausal\ symptoms) \pm (uterus) \pm (oral\ contraception)]$$

The second thing the nonprofessional woman see is hot flushes and night sweats or vasomotor symptoms. Some known factors affecting menopausal symptoms in women around the world are mentioned in paragraph 2.3.9. Briefly, culture and obesity are important.

In (NICE HRT 2015), (obesity) as a data creature was subsumed into (lifestyle changes) and was unrelated neither to (menopausal symptoms) nor

(outcome of menopausal symptoms). Similarly, (woman's baseline characteristics) was dissociated from (menopausal symptoms).

Data reflecting what the nonprofessional woman see regarding 'hot flushes and night sweats' gives the following in addition to others listed in paragraph 3.1.:

$$(menopausal\ symptoms) = (woman) - (HRT)$$

$$(menopausal\ symptoms) = (frequency\ hot\ flush) + (anxiety\ low\ mood) + (frequency\ sexual\ intercourse) + (muscle\ pain)$$

The (frequency hot flush) data creature was favored over (severity hot flush) and (night sweat) creatures in defining (vasomotor symptoms). The (vasomotor symptoms) creature is of importance in defining (HRT) for the healthcare professional in (NICE NG23 2015).

The (anxiety low mood) creature in (NICE HRT 2015) is made up by subtracting (depression) from (anxiety low mood), equating (depression) with (low mood), and assigning (low mood) a value of zero (0, nil, null).

(frequency sexual intercourse) is what it is. It is related to (vaginal dryness), (urogenital atrophy), and a 'urinary symptoms' creature, not present. However, both {urogenital atrophy} and {urinary incontinence} are both separate worlds of guidelines which the unknown user may refer to.

The (muscle pain) creature is composed of (sarcopenia) and (osteoporosis). Ageing related osteoporosis was relegated to {osteoporosis} and (sarcopenia) was assigned a value of zero (0, nil, null) in (NICE HRT 2015). In (NICE NG23) for healthcare professionals, the discussion of 'sarcopenia' is spurious. (osteoporosis) was equated with (fractures) in both guidelines.

The third and fourth things the nonprofessional woman see are vaginal dryness and sex drive, desire, or libido, which may be completely or partially lost. The (frequency sexual intercourse) creature is what it is, and is related to (vaginal dryness), (urogenital atrophy), (anxiety low mood), (CBT), as well as {urogenital atrophy} and perhaps {depression} outside (NICE HRT 2015). To reiterate:

$$(menopausal\ symptoms) = (woman) - (HRT)$$

In (NICE NG23 2015) for healthcare professional users, (low libido) is treated with (HRT) which may be systemic or local, estrogen-only, estrogen-and-progesterone combined, and which may or may not increase serum hormone levels as well as (testosterone). Also, (vaginal dryness) is equated with (urogenital atrophy).

The fifth datum entry seen by the nonprofessional woman is leaking urine. Both {urogenital atrophy} and {urinary incontinence} are removed from (NICE HRT 2015) data. Some kind of 'stress incontinence' creature is subsumed into (vaginal dryness) and (urogenital atrophy). Similarly in (NICE NG23 2015), leaking urine is relegated to (urogenital atrophy).

The sixth datum entry seen by the nonprofessional woman is bone thinning or osteoporosis. In (NICE HRT 2015) data, {osteoporosis} was removed and (osteoporosis) was equated with (fractures). Healthcare professionals are instructed through (NICE NG23 2015) to inform women that (HRT) with or without (oral contraception) is associated with (decreased risk of both osteoporosis and cardiovascular disease): there is no data in (NICE HRT 2015) to support this information.

In contrast, healthcare professionals are not instructed to inform women that (HRT) without (exercise) is associated with (loss of muscle mass). The (cost of exercise without HRT) was deemed greater than the (cost of exercise with HRT). Note HRT was subtracted from exercise in the comparison phrase. It was inferred by the author that (cost of informing women about exercise) was deemed greater than (benefit of exercise on osteoporosis), the only equation in blue paragraph 3.1.

The seventh datum entry seen by the nonprofessional woman is anxiety and low mood. In (NICE HRT 2015), the (anxiety low mood) creature was made up by subtracting (depression) from (anxiety low mood), equating (depression) with (low mood), and assigning (low mood) a value of zero (0, nil, null). In any case healthcare professionals may consider (CBT) if (anxiety low mood) and (menopausal symptoms) are strongly associated. Selective serotonin reuptake inhibitors are not considered except if {depression}.

The eighth entry a nonprofessional woman sees is no hormone test required before HRT. Equations describing (premature menopause) and its diagnosis data within the guidelines are discussed above.

The ninth is lifestyle changes and that was removed to {lifestyle changes}, (obesity) was subsumed into that, and the healthcare professional was not told to tell her that (HRT) without (exercise) is (loss of muscle mass).

Tenth is St John's wort and the healthcare professional is warned to warn that (St John's wort) is contraindicated in (breast cancer).

For the eleventh datum entry the nonprofessional woman see, data in (NICE HRT 2015) found that (black cohosh) and (HRT) are about as effective on (menopausal symptoms), allowing that (black cohosh) reduced (frequency hot flush) more than (HRT). However, due to standardization issues, (black cohosh) was not recommended. This is a narrative, the data is processed relative to (HRT) and as such (black cohosh) is not an element.

Similarly for all of isoflavones, acutherapy, homeotherapy, aromatherapy, bioidentical hormones, clonidine, gabapentin, are simply not elements of (HRT) and there is no data in those creatures, neither in (NICE HRT 2015) nor (NICE NG23 2015). As mentioned, (CBT) was more or less removed from (NICE HRT 2015), and surfaces in (NICE NG23 2015) with (anxiety low mood).

The twentieth thing seen by the nonprofessional woman is testosterone. The equations described by data including (testosterone) are that it is most effective on (frequency sexual intercourse).

The twenty-first datum entry for the nonprofessional woman is long term risks and benefits of HRT including hypertension, diabetes, breast cancer, so on. This is interesting.

In (NICE HRT 2015) data it was shown that:

- the risk of (HRT-related breast cancer) is smaller than the cost of (HRT-related breast cancer);
- the risk of (venous thromboembolism) and which included (deep venous thrombosis) and (pulmonary embolism) creatures is significantly present with (HRT). But it was greater than (risk with oral HRT), which was greater than (risk with transdermal HRT);
- the (absolute risk of cardiovascular disease while on HRT) was greater than (relative risk of cardiovascular disease while on HRT), which was greater than the (risk of stroke while on HRT), which was greater than the (risk of cardiovascular disease with oral HRT), which was greater than the (risk of cardiovascular disease with transdermal HRT);
- (HRT withdrawal) is associated with (increased risk of type 2 diabetes);
- (measuring blood glucose) equals (improved outcome for women on HRT);
- (cost of measuring blood glucose) was deemed greater than (cost of HRT-induced type 2 diabetes) and (risk of HRT-induced type 2 diabetes);

In other words, that there are risks of breast cancer, venous thromboembolism including deep venous thrombosis and pulmonary embolism, cardiovascular disease, stroke, and type 2 diabetes with HRT.

Interestingly, the above data in (NICE HRT 2015) did not communicate faithfully to (NICE NG23 2015). The healthcare professional was to inform the woman that:

- the risk of chronic heart disease without HRT is greater than the risk of chronic heart disease if she is on estrogen-only HRT;
- the risk of chronic heart disease if she is on estrogen-and-progesterone HRT is greater than if she is without HRT;
- the risk of stroke with oral HRT is about the same as risk of stroke in general, and which is negligible for woman less than sixty;
- some nonsense about dementia.

There is no data to support this information given to the woman by the healthcare professional. In moving from (NICE HRT 2015) to (NICE NG23 2015), not only were the data creatures cartoonified, they were

made up. Some creatures appear to have metamorphized into something unrelated to the hard numbers in (NICE HRT 2015).

Twenty-two is contraception and it gave a definition of (woman).

Twenty-three is stopping HRT and of course:

$$(withdrawal\ of\ HRT) = (menopausal\ symptoms)$$

Another equation describing what is seen regarding (HRT withdrawal) in (NICE NG23 2015) is:

$$(unexpected\ vaginal\ bleeding) \subset (endometrial\ cancer)$$

This is the only one subset $\subset$ symbol in (NICE NG23 2015) data, all the others are elements $\in$. While the unknown user may or may not be concerned with {urinary incontinence}, {depression}, {lifestyle}, so on, the healthcare professional here has to pull up the healthcare professional guideline version of {endometrial cancer} or {vaginal bleeding} unexpectedly. This is because:

$$\begin{aligned}(outcome\ of\ menopausal\ symptoms) \\ = (vaginal\ bleeding) \\ + (discontinuation\ of\ treatment)\end{aligned}$$

In other words, give HRT to all and the only things, really, to be concerned about are that if she stops taking it and if she develops endometrial cancer.

Twenty-four is referral which is two things in (NICE HRT 2015): (review) which should happen less than the (cost of HRT with continuation of symptoms); and (referral) which is to be considered if HRT produces side effects or if HRT is contraindicated.

5. Cui bono

What the woman sees is supported by data communicating:

(i) (woman) is (premature menopause) with or without (oral contraception) and (HRT).

(ii) If you have menopausal symptoms and are over 40 you will be offered HRT with or without 2 FSH samples.

(iii) A woman over 40 without (HRT) is (menopausal symptoms), premature or otherwise.

(iv) Menopausal symptoms of lost sexual desire, leaking urine, and vaginal dryness are addressed with HRT of one or two hormones and lubrication with or without hormones which may or may not increase serum hormone levels and to which testosterone is added to increase frequency of sexual intercourse.

(v) If you've had breast cancer we can still consider HRT and if you get breast cancer on HRT someone will pay for (breast cancer).

(vi) Your weight, past history including presence or absence of uterus, lifestyle, and so on, are not part of HRT without which you are (menopausal symptoms).

(vii) You can take HRT regardless of your condition and even if you get type 2 diabetes and hypertension while on HRT we can control it.

(viii) HRT increases your chances of getting stroke, embolism, and heart disease and maybe breast cancer; it has no effect on your bones, circulatory health, and completely unknown effects on your brain and we are going to suggest otherwise and misinform you.

(ix) Your diagnosis is the information you are receiving so the decision is yours.

These communications do not indicate a well-meaning physiological and clinical outlook. For the present, the activity of guideline creatures on (woman) will be referred to as FUKEM or Females Under faKtors Existing Metaphorically.

FUKEM is implemented in the zone of BUTS.

As shown in Figure 2., there are recognizable relationships between groups of data which the woman sees, and actual data which has gone into what the woman sees.

For example, the woman sees much data on lifestyle and alternative therapies when there is no data to support any of that in the guidelines of interest. This is a simple inverse relationship.

The woman sees data about risks and benefits which was altered from some kind of 'if you are overweight, prone to heart disease, have a history of anything ranging from hypertension to type 2 diabetes to breast cancer, then you really should not consider HRT' creature, to some kind of 'HRT is about as safe as crossing the road on a good day, is good for your heart and

bones, and maybe even your brain' creature. In moving from (NICE HRT 2015) to (NICE NG23 2015), creatures were perverted.

HRT or menopause data is an obvious zone of BUTS where in the hierarchy of evidence, (R)CTs and the network meta-analysis are king. So we are going to look at treatments BUT only if they were in (R)CTs against placebo. BUT only if they treat (menopausal symptoms) as we define them. BUT (vasomotor symptoms) are only (frequency hot flush). BUT (vaginal bleeding) and (discontinuation of treatment) are the only outcomes that matter. BUT they mattered on the short term and not the long. BUT there was bias in what was fed into…

And then we may move along the evidence hierarchy: BUT if network meta-analysis says no we will move things around. BUT then we can look at cohort studies. BUT our experience.

And if all else fails there are external factors: BUT black cohosh is not standardized.

These are physiological concerns which are moot because:

$$[woman] = [(premature\ menopause) \pm (oral\ contraception) \pm (HRT)]$$

The zone of BUTS used to maneuver (breast cancer) are frankly shocking.

On the other hand, BUT acutherapy homeotherapy aromatherapy isoflavones *etc*…have no data.

As to risks BUT if you are controlled, BUT are you taking one or two or three hormones BUT which way are you taking them BUT here are the tables of evidence with NO DATA mostly and but make up your own mind.

"…The menopause is a natural milestone in women's lives and can be seen as the gateway to further aging processes…" (NICE HRT 2015) page 65.

"…Individualised care…This guideline offers best practice advice on the care of women in menopause. Treatment and care should take into account individual needs and preferences. Women should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. The Guideline Development Group followed the recommendations set out in the NICE guideline on patient experience which offers evidence- based advice on ensuring a good experience of care for people who use adult NHS services…Recommendations…Adopt an individualised approach at all stages of diagnosis, investigation and management of menopause. Follow recommendations in the NICE guideline on patient experience in adult NHS services…" (NICE HRT 2015) page 68.

This is some kind of (fascism) creature.

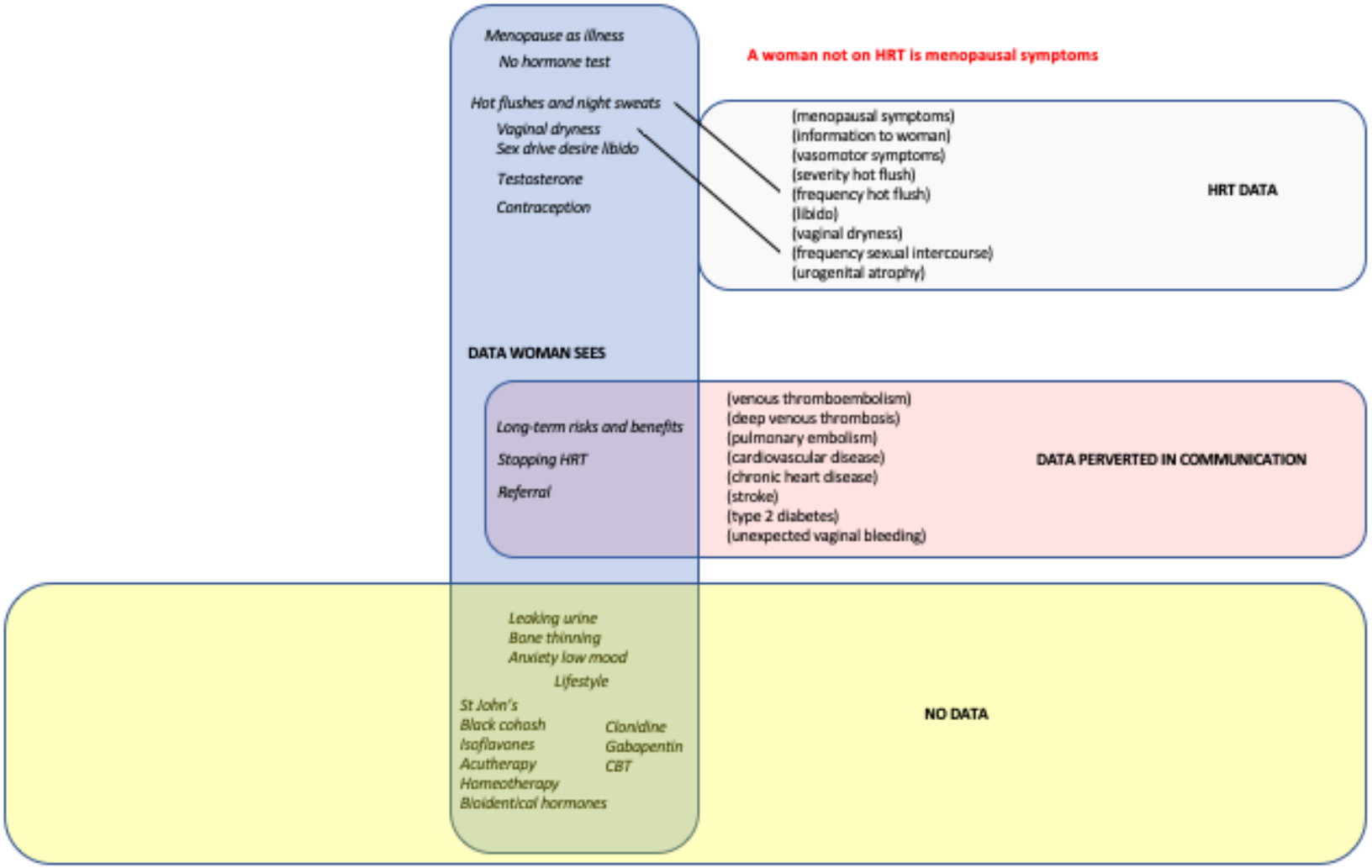
Menopause as illness
No hormone test
Hot flushes and night sweats
Vaginal dryness
Sex drive desire libido
Testosterone
Contraception
A woman not on HRT is menopausal symptoms
(menopausal symptoms)
(information to woman)
(vasomotor symptoms)
(severity hot flush)
(frequency hot flush)
(libido)
(vaginal dryness)
(frequency sexual intercourse)
(urogenital atrophy)
HRT DATA
DATA WOMAN SEES
Long-term risks and benefits
Stopping HRT
Referral
(venous thromboembolism)
(deep venous thrombosis)
(pulmonary embolism)
(cardiovascular disease)
(chronic heart disease)
(stroke)
(type 2 diabetes)
(unexpected vaginal bleeding)
DATA PERVERTED IN COMMUNICATION
Leaking urine
Bone thinning
Anxiety low mood
Lifestyle
St John's
Black cohash
Isoflavones
Acutherapy
Homeotherapy
Bioidentical hormones
Clonidine
Gabapentin
CBT
NO DATA

Figure 2.

6. Clustering FUKEMs and zones of BUTS

The first thing a woman see when she logs onto RCOG and NICE websites on menopause is that, due to ageing, hormones need to be topped up with HRT. The source of this FUKEM is in (NICE HRT 2015) zones of BUTS data. Once this data is resolved, the 'menopause as illness' FUKEM is explained. If you are complaining of menopausal symptoms, it is because you are a woman without HRT. A woman is something which has lost fertility prematurely, with or without oral contraception and HRT.

From a physiological perspective, this is a FUKEM experienced by unknown user in (NICE HRT 2015) zones of BUTS, not immediately related to the FUKEM experienced by the woman in the RCOG, NICE, NHS, and WHC websites, and other zones of BUTS .

Each FUKEM has its own zones of BUTS which are related. For the woman and unknown user, these FUKEMS are mostly in the head.

The healthcare professional experiences a sandwich kind of FUKEM. Frankly, I cannot see how any professional can work with (NICE NG23 2015), let alone health. [14] This is the FUKEM in the clinic. The FUKEM is also in the head, of course, as well as the clinic.

FUKEM experienced in the clinic has zones of BUTS which, with little theoretical effort, spiral beyond imagination, which is where they exist.

As we move from what appears to the woman, to what appears in (NICE HRT 2015), to what appears in (NICE NG23 2015), to what might appear in reality, we cross horizontally and longitudinally through zones of BUTS, and FUKEMs all the way. This will be encapsulated in CLUSTER FUKEM BUTS.

What is the source of the FUKEM experienced by unknown user, and so the source of the FUKEM experienced by nonprofessional woman? And, if we step back, by what entity are CLUSTER FUKEM BUTS generated? Obviously, the answer is 'not just pharmaceutical companies', check the list of stakeholders. Importantly, this is a public health system.

[14] A good doctor uses paperwork to help the patient. However, in the present, (diagnosis) = (information to patient).

7. The Neoliberal Manifesto

There is something terrifying about defining (woman) in (NICE HRT 2015) as:

$$[woman] = [(premature\ menopause) \pm (oral\ contraception) \pm (HRT)]$$

The creatures generated by (NICE HRT 2015), such as (urogenital atrophy) and (vasomotor symptoms) are, from a physiological perspective terrifying in a comic way: after the first shock they look ridiculous and when touched their stuffing clatters wanking toyishly. Where is the terror in the definition above?

From any psychology perspective, deep or shallow, a psyche seen as a cannister which needs to be topped up, lubricated, and fucked frequently is bound to be terrified. The psyche of the healthcare professional is terrified in glorified white coats and other uniforms, if not from the sheer amount of biological and administrative data, and not from the malpractice claims, and not from what appears to be an impossible task of individualizing care in a system of individualized care, then from being a mere conduit (diagnosis) = (information to patient).

The terror in the creatures of (NICE HRT 2015) was described by Eric Arthur Blair pen name George Orwell. It concerns the nature of language.

As with other words in the English language, /woman/ can be noun and verb /womanizing/stop mothering me/man up/.[15] Google it.

[15] We had previously defined *weleyyah* in (Helmy and Frerichs 2013) as "…a derogatory term referring to a woman of unsavory social origin and of quarrelsome, noisy character…" in reference to Susanne Mubarak. In the authors' defense, a full definition was ommitted for word count considerations. That was a phenomenonological definition of *weleyyah* as used in colloquial Egyptian. A linguistic definition is now in order. WA-LE-YAH is the trilateral root word of *weleyyah* in Arabic. WA-LE-YAH denotes /closeness /proximity /protection /strong love /friendship /rain which comes after rain /the opposite of enemy. *Wal-ey (amr)* is /parent/she who is responsible for the matters pertaining to so and so/ custodian/. *Welaa-yah* is /nation /state/. *Waaly* is /ruler /leader /he who is responsible for the affairs of state /prince regent/ so on. *Waly-3ahd* is /successor/. *Wall-la* is turned around and fled or ran away– it is not uncommon that the same trilateral root produces polar opposites. *Al-Waly*, *Al-Mawlaa,* and *Al-Waaly* are names of God. While *weleyyah* comes from WA-LE-YAH, in colloquial Egyptian Arabic, which simplifies and slurs Arabic proper, *weleyyah* is also (with a humorous and foul outlook) related to WAL-WA-LAH /he wailed like a *weleyyah*/. WAL-WA-LAH is interesting in the Arabic lexicon for two reasons. First, it is one of the less common quadrilateral root words. Second, it is onomatopoeic: WAL WEL WAL WEL WALAAAAHWEE! So a *weleyya* in Egyptian colloquial is etymologically both, /she who is responsible /she who is responsible for upbringing and the order of society /custodian /the loved close friend /protector /defender , as well as /she who wails/.

The terror in the (NICE HRT 2015) creatures is that they noun-ify the verb, and verb-ify the noun. Or Objectivize the Subjective and Subjectify the Objective. We probably do that all the time and not only as children, the problem here is it's being done for us with malintent.

The creatures interact with reality in what the woman sees, what the healthcare professional sees, and what unknown user sees.

What woman sees is related to what unknown user sees in the following ways:

(i) Alternative therapies are inversely related to actual data;

(ii) Long term risks and benefits and HRT withdrawal is perversely related to actual data;

(iii) Menopausal symptoms are related to data in (NICE HRT 2015) defining (woman) as (menopausal symptoms) without (HRT).

What the woman sees in the clinic is what the healthcare professional sees, which is related to what unknown user sees by:

$$(diagnosis) = (information\ to\ woman)$$

The creatures which were put together to stuff (information to woman), which is self-diagnosed, are tools of violence and deception. The creatures, which are used as tools, are chimeras of unphysiological/unsociological data, and symbols/sounds used in society to tell stories and make decisions.[16]

At one end, the creatures interact with reality in what the woman sees. At the other, as far as we can see, the creatures interact with reality in what unknown user sees. In the clinic, creatures interact with reality presumably guided/recommended by clusters of CLUSTER FUKEM BUTS.

There is a reality for developers, with whom the creatures are also interacting.

Knowledge is controlled by institutions including religious, there is nothing new about that. And they put our languages down on paper or something, that's some kind of control whether we like it or not. What terrified Orwell is that language is actively and Objectively controlled by apes who believe they can.

A noun tells you what you are, and a verb tells you what you're doing. (NICE HRT 2015) creatures are terrifying because they don't know what they are, and they don't know what they're doing.

[16] To reiterate, physiology/sociology is well-meaning and not, for example, explored from the perspective of HRT.

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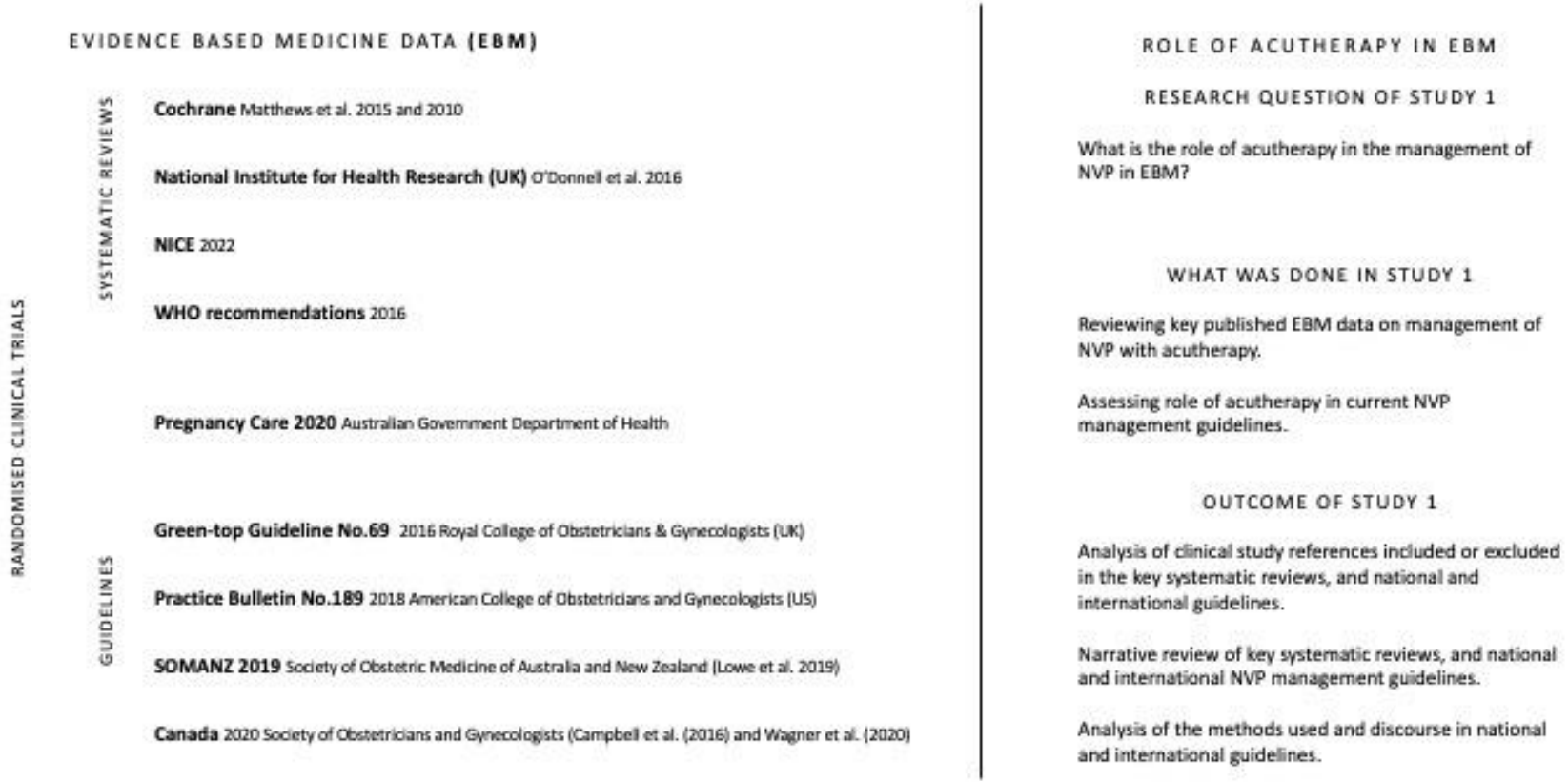
Study 1

Graphical Abstract



Disambiguation

In the present work, *acutherapy* refers to acupuncture, acupressure, and acustimulation.

Acupuncture involves puncturing the skin with a needle at a point recognized by Traditional Chinese Medicine (TCM).

Acupressure involves applying pressure by any means to a point on the body recognized by TCM.

Acustimulation involves passing an electrical current by any means through a point recognized by TCM.

(R)CT refers to a clinical trial whether deemed randomized or not.

Research question, Aims, and Objectives

Research question Study 1

What is the role of acutherapy in the management of NVP in EBM?

Aims

Reviewing key published clinical trial data on management of NVP with acutherapy.

Assessing role of acutherapy in current NVP management guidelines.

Objectives

Analyse key published systematic reviews of clinical trial data.

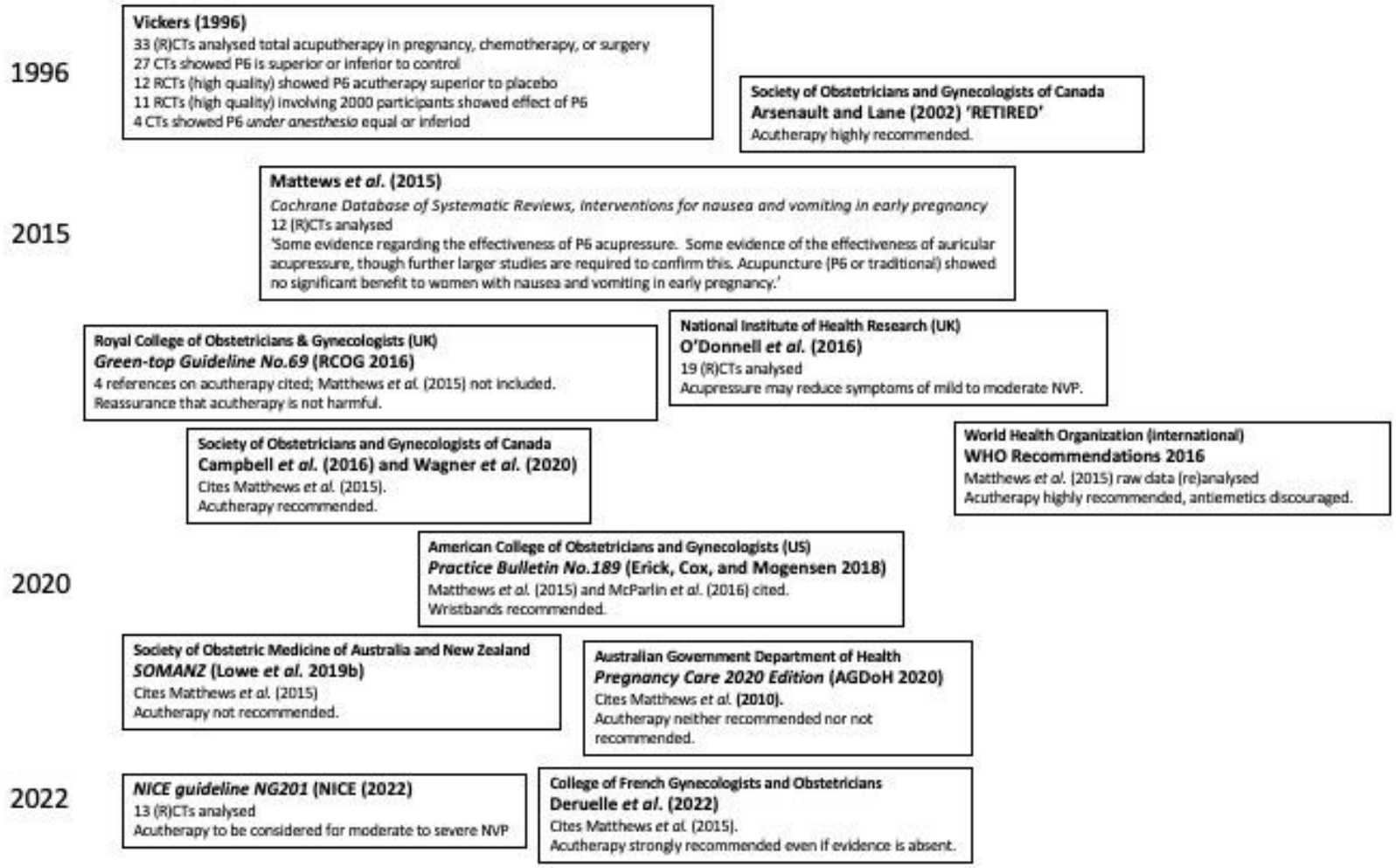
Analyse national and international guidelines on management of NVP.

Outcomes

Analysis of references in the key systematic reviews, and national and international guidelines.

Review of key EBM of NVP management with acutherapy data, and national and international NVP management guidelines.

Analysis of the methods used and discourse in national and international guidelines



Reviewing key published clinical trial data on management of NVP with acutherapy

Studies analysed by Matthews et al. (2015) and O'Donnell et al. (2016)

Clinical trials whether deemed randomized or not, or (R)CTs, found by Cochrane *Database of Systematic Reviews, Interventions for nausea and vomiting in early pregnancy*, cited in the present work as (Matthews et al. 2015) are in Table 1. Twelve (R)CTs were included for analysis of acutherapy in management of NVP by Matthews et al. (2015). Of those, no online English full text or no access was possible for seven (R)CTs. Of the remaining five, two (R)CTs showed that acupressure was no better than sham, one (R)CT showed that acupuncture is better than sham, one (R)CT showed that ginger is better than acupuncture, and the remaining 'group' of references are inconclusive.[17] Briefly, studies analysed by Matthews et al. (2015) for acutherapy management of NVP are inaccessible, inconclusive, irrelevant, or combinations thereof.

(R)CTs found by the National Institute for Health Research (UK) *Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment* (cited in the present work as (O'Donnell et al. 2016) are in Table 2. This research is published as an article (McParlin et al. 2016). A total of 19 (R)CTs were analysed.

Findings regarding acutherapy management of NVP in Matthews et al. (2015) and O'Donnell et al. (2106) are summarized in the Figure above.

Studies not in the analysis by Matthews et al. (2015)

Eight studies all published before 2009 were missed by Matthews et al. (2015) and analysed by O'Donnell et al. (2016). One study judged by O'Donnell et al. (2016) to have a high risk of bias was included in analysis by Matthews et al. (2015), and one study judged by O'Donnell et al. (2016) to have a low risk of bias was excluded from analysis by Matthews et al. (2015). However, the reason(s) for exclusion from analysis by Matthews et al. (2015) does not appear consistent, particularly when compared and contrasted with features of studies that were included for analysis for example see footnotes.

[17] Matthews et al. (2015) refer to more than one publication using the same citation as shown in Table 1.

NICE studies

Studies *included in analysis* in the systematic review by the National Institute for Health and Care Excellence (UK) to develop the *NICE guideline NG201* (NICE 2022) are in Table 3. All but one of these studies were *Excluded After Analysis* and so are labelled *EAA* in the Tables below. Studies that were *Excluded Before Analysis* by NICE are labelled *EBA* in the Tables below.

Studies not cited by Matthews et al. (2015), O'Donnell et al. (2016), nor NICE (2022)

These are in Table 4. The reader's attention is gently drawn to (Vickers 1996) published before 2015, and (Lu et al. 2021) published after 2015.

Table 1. (R)CTs included and excluded in the analysis by (Matthews et al. 2015)					
INCLUDED (in order of appearance in the text page 8)					
#	**Article**	**Conclusion of the article**	**Remark**	**NICE?**[18]	**Referred as**[19]
1	(Belluomini et al. 1994)	P6 acupressure reduces NVP symptoms not vomiting	No full text online?	EAA	Belluomini 1994
2	(KHAVANDIZADEH and Mahfouzi 2010)	P6 acupressure reduces severity of NVP	No full text online?	EBA	Khavandizadeh 2010
3	(Norheim et al. 2001a) (Norheim et al. 2001b)	Consider acupressure before drugs for morning sickness	Article not in English?	EBA	Norheim 2001
4	(O'Brien, Relyea, and Taerum 1996)	No benefit of P6 acupressure. No control group.	Not open access?	EBA	O'Brien 1996
5	(Werntoft and Dykes 2001)	P6 acupressure reduces NVP.	No full text online?	EAA	Werntoft 2001
6	(Jamigorn and Phupong 2007)	Acupressure therapy is not more effective than vitamin B6.	Not open access?	EBA	Jamigorn 2007

[18] In this column, *EBA* denotes that the article was *Excluded Before Analysis* by NICE, see Appendix K pages 204-217 of (NICE 2021a), or the online version (NICE 2021b). Links provided below. *EAA* denotes that the article was *Ecluded After Analysis*, which are all but one of the references listed in Table 3. 'No' denotes that the article was not found by NICE directly, and may have been found by NICE developers indirectly through cross-check of references excluded from the study.

[19] 'Referred as' in this column is how an article or more was referred to in (Matthews et al. 2015) References pages 25-27 or online here. Note that all these references were listed in (Matthews et al. 2015) as "…{published data only}…" (*sic, ibid*).

7	Saberi F. Comparison of acupressure and ginger in the treatment of nausea and vomiting of pregnancy. IRCT: Iranian Register of Clinical Trials (www.irct.ir) [accessed 20 September 2011]2011.		'Last accessed 2011'.[20] No link?	No	Saberi 2014
	(Saberi et al. 2013)	Ginger is more effective than acupressure to relieve mild to moderate NVP.			
	(Saberi et al. 2014)	Ginger was effective for the relief of mild to moderate NVP.	Irrelevant and perhaps duplicate.	EAA	
8	Lamyian M. Evaluation of the influence of KID 21(youmen) point acupressure on nausea and vomiting of pregnancy. IRCT: Iranian Register of Clinical Trials (www.irct.ir) [accessed 30 April 2013]2013.		'Last accessed 2012.' No link	No	Rad 2012
	Rad MN. Evaluation of the influence of KID 21 (youmen) point acupressure on nausea and vomiting of pregnancy. IRCT Iranian Registry of Clinical Trials (www.irct.ir) [accessed 6 December 2010]2010.				
	(Rad et al. 2012)	Acupressure on KID21 point is more effective than sham acupressure in reduction of NVP.		EAA	
9	(de Veciana et al. 2001)	Nerve stimulation does not improve symptoms and decreases vomiting bouts.	Abstract only?	No	Rosen 2003
	(Miller et al. 2001)				

[20] 'Last accessed' data is from (Matthews et al. 2015) pages 25-27.

	(Rosen et al. 2003)	Nerve stimulation therapy is effective in reducing nausea *and* vomiting and promoting weight gain.	No full text online or not open access?		
10	(Puangsricharern and Mahasukhon 2008)	Auricular acupressure therapy does not relieve NVP.		EAA	Puangsricharern 2008
11	(Knight et al. 2001)	Acupuncture as effective as sham in NVP treatment.		EAA	Knight 2001
12	(C Smith and Crowther 2002)	Sham acupuncture is a credible control.		No	Smith 2002
	(Caroline Smith, Crowther, and Beilby 2002b)	Consider acupuncture for NVP.		EAA	
	(Caroline Smith, Crowther, and Beilby 2002a)	No serious adverse effects with acupuncture in early pregnancy.		No	
	Smith C, Crowther C, Beilby J. Women's experiences of nausea and vomiting in early pregnancy. 2nd Annual Congress of the Perinatal Society of Australia & New Zealand; 1998 March 30-April 4; Alice Springs, Australia. 1998:142.		?	No	
13	(范永军 1995)	'Moxibustion therapy is superior to Chinese drug in treatment of pregnant vomiting'.	Citation? Chinese?	No	Fan 1995
	(Fan, Zhu, and Fu 1995)				

EXCLUDED by (Matthews et al. 2015) pages 28-29 or click here. See also Characteristics of excluded studies page 75.					
#	**Article**	**Conclusion of the article**	**Remarks**	**NICE?**	**Referred as**
14	(Anjum et al. 2002)	Morning sickness acupressure	Citation	No	Anjum 2002
15	(Bayreuther, Pickering, and Lewith 1994)	P6 acupressure better than sham.	Included in (O'Donnell et al. 2016) study.	No	Bayreuther 1994
16	(Can Gürkan and Arslan 2008)	P6 acupressure relieves symptoms with or without placebo.		EBA	Can Gurkan 2008
17	(De Aloysio and Penacchioni 1992)	Acupressure relieves NVP	Cross-over	EBA	De Aloysio 1992
18	(Dundee et al. 1988)	P6 acupressure therapeutic in NVP	Why excluded?[21] Appears good.	EBA	Dundee 1988
19	(Heazell et al. 2006)	No effect of acupressure	Why excluded?[22]	EAA	Heazell 2006

[21] The reason given on page 75 is "…Not an RCT; women allocated to groups by day of the week; non-responders replaced in treatment group…"

[22] "…Severe symptoms, in-patient; hyperemesis gravidarum implied (severe symptoms plus ketonuria)…" (?)

20	(Hyde 1989)	Acupressure relieves depression, anxiety, and behavioral dysfunction, and nausea in NVP	Cross-over	EBA[23]	Hyde 1989
21	(Ozgoli, Shahbazzadegan, and Rassaian 2007)	Wristband with or without P6 pressure effective for NVP		No	Shahbazzadegan 2007
	Shahbazzadegan S. Investigation the trend of pregnancy nausea and vomiting treatment using acupressure wristband. IRCT: Iranian Register of Clinical Trials (http://www.irct.ir) (accessed 30 April 2013)2006.				
22	(Steele et al. 2001)	Wristband brand effective for NVP		EBA	Steele 2001

[23] NICE (2022a) also exclude studies for being cross-over. However, this was excluded for being 'duplicate' page 209-210.

Table 2. (R)CTs analysed by (O'Donnell et al. 2016) in order of appearance in the text.				
Judged 'low risk of bias' by O'Donnel *et al*. 2016				
#	**Article**	**Matthews**[24]	**NICE**[25]	**Referred as**[26]
1	(Bayreuther, Pickering, and Lewith 1994)	Yes, excluded	No	61
2	(Belluomini et al. 1994)	Yes, included	EAA	62
3	(Carlsson et al. 2000)[27]	No	No	66
4	(Jamigorn and Phupong 2007)	Yes, included	EBA	80
5	(Knight et al. 2001)	Yes, included	EAA	83
6	(Rad et al. 2012)	Yes, included	EAA	91
7	(Rosen et al. 2003)	Yes, included	No	98
8	(Caroline Smith, Crowther, and Beilby 2002b)	Yes, included	EBR	101

[24] In this column, the following question is answered: Was this article found by (Matthews et al. 2015)? If *Yes*, was it included or excluded?

[25] In this column, *No* means the article was not directly found by NICE, and may have been indirectly found through cross-check of other references. Note that on page 213 of (NICE 2021a) it states that O'Donnell et al. (2016) references were checked and no additional studies identified; *EBA* denotes that the article was *Excluded Before Analysis* by NICE, see Appendix K pages 204-217 of (NICE 2021a), or the online version (NICE 2021b). Links provided below; and *EAA* denotes that the article was *Ecluded After Analysis.*

[26] These numbers refer to the reference number in (O'Donnell et al. 2016) pages 173-182 or click here.

[27] P6 acupuncture + standard treatment faster recovery from HG compared to sham

Judged 'high risk of bias' by (O'Donnell et al. 2016)				
#	**Article**	**Matthews**	**NICE**	**Referred as**
9	(Mao and Liang 2009)	No	EBA	87
10	(Neri et al. 2005)	No	No	94
11	(Werntoft and Dykes 2001)	Yes, included	EAA	111
12	(Zhang 2005)	No	No	115
13	(Markose, Ramanathan, and Vijayakumar 2004)	No	No	124
Judged 'unclear' by O'Donnell *et al.* (2016)				
14	(Can Gürkan and Arslan 2008)	Yes, excluded	No	43
15	(A. Evans et al. 1993) and (A. T. Evans et al. 1994)[28]	No	No	73
16	(Heazell et al. 2006)	Yes, excluded, see footnotes	Yes	78
17	(Hsu et al. 2003) Citation?	No	No	79
18	(Steele et al. 2001)	Yes, excluded	No	104
19	(de Veciana et al. 2001)	No	No	109

[28] Evans *et al.* (1993) which appears to be an abstract only is cited in O'Donnell *et al.* (2016). I found Evans *at al.* (1994) which appears not to be open access. The title of both is *Suppression of Pregnancy-Induced Nausea and Vomiting With Sensory Afferent Stimulation*. It was reported that NVP effectively improved with treatment compared to placebo device.

Table 3. Articles *Excluded After Analysis (EAA)* in NICE (2022)		
Articles in random order	**Grouped in NICE as**	**Total number of articles**
(Habek et al. 2004); (Heazell et al. 2006); (Adlan, Chooi, and Mat Adenan 2017)	Acupressure or acupuncture for moderate to severe NVP	3
(Belluomini et al. 1994); (Knight et al. 2001); (Werntoft and Dykes 2001); (Caroline Smith, Crowther, and Beilby 2002b) (Puangsricharern and Mahasukhon 2008); (Rad et al. 2012); (Saberi et al. 2014); (Galeshi et al. 2020); (Ghule and Sureshkumar 2020) (Mobarakabadi, Shahbazzadegan, and Ozgoli 2020)[29]	Acupressure or acupuncture for mild to moderate NVP	10

[29] In addition: "…One RCT reported an 8-arm unpublished trial from the 1970s that aimed to evaluate the efficacy of (Zhang 2017) pyridoxine hydrochloride and doxylamine succinate. The 8 arms of the trial were pyridoxine hydrochloride, a histamine H1-receptor antagonist (doxylamine succinate), a combination of pyridoxine hydrochloride and doxylamine succinate, and a placebo. The other arms of the trial were dicyclomine, a combination of dicyclomine and pyridoxine hydrochloride, a combination of dicyclomine and doxylamine succinate, and a combination of dicyclomine, pyridoxine hydrochloride, and doxylamine succinate, all of which were not interventions of interest for this review…" page 8 of (NICE 2021a).

Table 4. Acutherapy for NVP systematic reviews, RCTs, and clinical trials not cited by O'Donnell et al. (2016), Matthews et al. (2015), nor NICE (2022), or else found and excluded by NICE (2022) noted below					
#	**Article**	**Type**[30]	**Incl**[31]	**Conclusion of the article**	**Remarks**
PUBLISHED AFTER 2015					
1	(Yue et al. 2022)	SR	13	This systematic review reveals that the efficacy of auricular acupressure in managing NVP is insufficient and the efficacy of auricular acupressure for treating NVP remains limited.	
2	(Lu et al. 2021)	SR	16	'Our study suggested that acupuncture was effective in treating HG. However, as the potential inferior quality and underlying publication bias were found in the included studies, there is a need for more superior-quality RCTs to examine their effectiveness and safety. PROSPERO registration number: CRD42021232187.'	Chinese articles analysed largely. Includes ketonuria.
7	(Mobarakabadi, Shahbazzadegan, and Ozgoli 2020)	RCT	75	P6 acupressure with or without placebo effective for NVP. Wristband brand recommended.	EAA and referred to as 2019

[30] *SR* denotes systematic review, *RCT* randomized clinical trial, and *CT* clinical trial.

[31] The number in this column denotes the number of studies included in an SR, or the number of participants in an RCT or CT.

8	(Galeshi et al. 2020)	RCT	?	Pressure on P6 and KID21 points has no advantage over each other in the treatment of NVP, but acupressure is an effective, complication-free, inexpensive and accessible treatment for this complication	EAA
9	(Ghule and Sureshkumar 2020)	?	?	The results obtained from this study showed that the Accu TENS with Accu band can be easy to perform, least expensive, feasible and most efficient management strategy for reducing nausea, vomiting and retching, weight gain and enhancing the quality of life of individuals with early pregnancy	EAA
	(Kirca and Gul 2020)	CT	140	'Statistical results have provided that acupressure taught to women was found to be highly effective in reducing pregnancy-induced nausea and vomiting.	
10	(Tsakiridis et al. 2019)	SR	3	ASOG, SOGC, RSOG compared. Concludes: 'Evidence-based medicine may lead to the adoption of an international guideline for the management of NVP, which may lead to a more effective management of that entity.' (*sic*)	

11	(McParlin et al. 2016)	SR[32]	8[33]	This is quoted in full in footnote[34]	EBA
PUBLISHED BEFORE 2015					
12	(Vickers 1996)	SR	33	This is quoted in full in footnote[35]	
13	(Arsenault and Lane 2002)	SR[36]		RETIRED. Relevant text is quoted in footnote[37]	

[32] This is also a guideline.

[33] These are probably articles #1 to #8 in Table x., or those judged low risk of bias by O'Donnell et al. (2016), I did not cross-check.

[34] "…In summary for acupressure: treatment with acupressure was associated with symptom improvement for mild cases (level A, class IIa). For nerve stimulation: evidence indicates treatment may be considered, but the benefit was unclear (level B, class IIb). For acupuncture: the benefit was unclear (level A, class IIb)…"

[35] "…The effects of acupuncture on health are generally hard to assess. Stimulation of the P6 acupuncture point is used to obtain an antiemetic effect and this provides an excellent model to study the efficacy of acupuncture. Thirty-three controlled trials have been published worldwide in which the P6 acupuncture point was stimulated for treatment of nausea and/or vomiting associated with chemotherapy, pregnancy, or surgery. P6 acupuncture was equal or inferior to control in all four trials in which it was administered under anaesthesia; in 27 of the remaining 29 trials acupuncture was statistically superior. A second analysis was restricted to 12 high-quality randomized placebo-controlled trials in which P6 acupuncture point stimulation was not administered under anaesthesia. Eleven of these trials, involving nearly 2000 patients, showed an effect of P6. The reviewed papers showed consistent results across different investigators, different groups of patients, and different forms of acupuncture point stimulation. Except when administered under anaesthesia, P6 acupuncture point stimulation seems to be an effective antiemetic technique. Researchers are faced with a choice between deciding that acupuncture does have specific effects, and changing from 'Does acupuncture work?' to a set of more practical questions; or deciding that the evidence on P6 antiemesis does not provide sufficient proof, and specifying what would constitute acceptable evidence…" (Vickers 1996).

[36] This is also a guideline.

[37] "…**Recommendations:** I. Dietary and lifestyle changes should be liberally encouraged, and women should be counselled to eat whatever appeals to them. (III-C); 2. Alternative therapies, such as ginger supplementation. acupuncture. and acupressure, may be beneficial. (I-A); 3. A doxylamine/pyridoxine combination should be the standard of care since it has the greatest evidence to support its efficacy and safety. (I-A); 4. H_I receptor antagonists should be considered in the management of acute or breakthrough episodes of NVP. (I-A); 5. Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. (I-A); 6. Phenothiazines are

14	(Duke and Don 2005)	SR	-	REMOVED	
15	(Zhang 2005)	CT	150	Compares acu-p, Chinese medicine drug, and Western medicine drug. Concludes: 'Acup-moxibustion is the best method for hyperemesis gravidarum'.	Article in Chinese.
16	(Helmreich, Shiao, and Dune 2006b)	SR	22	This meta-analysis demonstrates that acupressure and ETS had greater impact than the acupuncture methods in the treatment of NVP. However, the number of acupuncture trials was limited for pregnant women, perhaps because it is impossible to self-administer the acupuncture and thus inconvenient for women experiencing NVP as chronic symptoms.	Not open access? EBA from NICE[38]
17	(Lee and Frazier 2011)	SR	?	Acupressure may be a useful strategy for the management of multiple symptoms in a variety of patient populations, but rigorous trials are needed. Inclusion of acupressure as an intervention may improve patient outcomes.	Includes chemotherapy.

safe and effective for severe NVP. (I-A); 7. Metoclopramide is safe to be used for management of NVP, although evidence for efficacy is more limited. (11-2D); 8. Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. (I-B); 9. When NVP is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken. (III-A) … **ACUPUNCTURE AND ACUPRESSURE** Stimulation of the P6 (Neiguan) point, located three-fingers' breadth proximal to the wrist, has been used for thousands of years by acupuncturists to treat nausea and vomiting from a variety of causes. Though there are no theoretical concerns about the safety of acupressure in pregnancy, efficacy of P6 acupressure is difficult to prove because it is impossible to perform a true double-blind trial compared with no intervention. Nonetheless, non-blinded RCTs have demonstrated a decrease in "persisting nausea" by at least 50%.11 Bands worn on the wrist to apply acupressure may also be helpful (citation to: Jewell D.Young G.lnterventions for nausea and vomiting in early pregnancy (Cochrane Review). ln: The Cochrane Library. Issue 4.2000. Oxford: Update Software)…" (emphasis in the original, Arsenault and Lane 2002, pages 817, 819, and 823).

[38] Nor could I access full text for (Shiao and Dibble 2006) the first author of whom is co-author on Helmreich, Shiao, and Dune (2006), and which is published in the same volume of *Explore* journal.

					EBA from NICE
18	(Sinha et al. 2011)	RCT	340	In this study acupressure wristbands applied bilaterally did not reduce the incidence of nausea and vomiting during labour and delivery	

Assessing role of acutherapy in current NVP management guidelines

Six current national level guidelines and one international guideline were analysed to assess the role played by acutherapy in management of NVP, discussed below and summarized in figure and graphical abstract above. To assess the role of acutherapy in a guideline, the following was done:

i. All references to acutherapy in a guideline were analysed, notably against EBM systematic reviews data presented in the preceeding section of the present work. Please note this includes all references to acutherapy in a guideline, the justification being that *acutherapy for NVP management* in a guideline is contextualized within a broader *acutherapy for NVP and other conditions* in the same guideline.

ii. Eight yes-or-no questions were asked under the heading ACURITE, these questions are listed on the next page. Briefly, the following was quantified: accurateness of a reference (was the reference used published within ten years of writing the guideline? Was the reference used about acutherapy in NVP?); usability of the guideline for acutherapy management of NVP (was there a description or treatment algorithm that includes acutherapy?); and consistency of the guideline with regards acutherapy (was acutherapy recommended? If so, is it in the treatment algorithm or is there a description?).

iii. The following question is answered: What is the guideline telling the user to do about managing NVP? This is given in a synopsis at the end of a guideline analysis.

iv. Analysis of methods used by, and discourse in the guidelines, to assess the role of acutherapy in current national and international guidelines concerned with pregnancy and NVP.

The eight yes-or-no questions that were asked under the heading *ACURITE* are (point (ii) above):

1. Was acutherapy discussed in the text of the guideline? If *Yes*, were the references used in the discussion of acutherapy:
2. …published within ten years from the date of the publication of the guideline? AND …about NVP, or about chemotherapy, surgery, motion sickness, so on, as well as NVP?[39] For example, a 1994 reference in a 2016 guideline is *ACURITE No.*
3. Was an acutherapy method described in the text?
4. Was acutherapy recommended? If *Yes*:
5. …with what grade?
6. Is acutherapy mentioned in the guideline's treatment algorithm?

Together, these questions work towards answering:

7. Can this guideline be used to manage NVP with acupuncture? For example, for a guideline with a brief acutherapy description, or for a guideline where acutherapy is mentioned in the treatment algorithm, the answer is *Yes.*
8. Is the guideline consistent regarding NVP acupuncture management? For example, for a guideline which recommends acutherapy and neither gives a description nor mentions acutherapy in the treatment algorithm, the answer is *No*. As another example, for a guideline which does not recommend acutherapy, and does not give a description nor mentions acutherapy in the treatment algorithm, the answer is *Yes.*

[39] Or something completely different. An underlying assumption here is that guideline developers would have had access to Mattews et al. (2015) at the time the guideline was published, and certainly to Matthews et al. (2010).

Green-top Guideline No.69

GUIDELINE ANALSIS #1	
Published in	UK
Published by	Royal College of Obstetricians & Gynaecologists
Publication name	*Green-top Guideline No.69*
Publication date	2016
Cited here as	(RCOG 2016)
Link to pdf	Click here.
Link to website	Click here.

ACURITE for *Green-top Guideline No.69*		
Is acupuncture discussed in the text?		Yes
	With ACURITE references?	No
	With acupuncture method description?	No
Was acupuncture recommended?		Yes
	With what grade?	B
Is acupuncture in the treatment algorithm?		No
Can this guideline be used to manage NVP with acupuncture?		No
Consistent regarding NVP acupuncture management?		No

A role for acupuncture in *Green-top Guideline No.69*?

Under "…Acustimulations – acupressure and acupuncture…", it states, "…Women may be reassured that acustimulations are safe in pregnancy. Acupressure may improve NVP…" (RCOG 2016, page 4). It was given grade of recommendation B.[40] However, in the "…Treatment algorithm for NVP and HG…" (page 26), there is no mention of acupressure nor acupuncture. 'Acustimulations' is discussed in a paragraph on page 12 and four references are mentioned, discussed here in Table 5. Neither Matthews et al. (2015) nor Matthews et al. (2010) are cited in the relevant text. *Green-top Guideline No.69* developers were able to refer to (Belluomini et al. 1994) and not to (Vickers 1996). Briefly, it does not appear that effort was made to include more robust clinical trial data available to the developers of *Green-top Guideline No.69* at the time of its writing in 2016.

***Green-top Guideline No.69* treatment algorithm for NVP and HG[41]**

In this *Guideline*, 'diagnosis is by exclusion of other causes'. 'Initial assessment' includes PUQE score and for 'clinical complications (dehydration, electrolyte imbalance, weight loss)', as well as 'offer advice and support'. One of three management outcomes then becomes possible:

(i) 'antiemetics in community and lifestyle and dietary changes'; or

(ii) 'ambulatory daycare management (saline, antiemetics, and thiamine) until no ketonuria'; or

(iii) 'inpatient management' which is 'thromboprophylaxis, multidisciplinary team approach and consider steroids' (RCOG 2016, page 26). A multidisciplinary team may include "…midwives, nurses, dieticians, pharmacists, endocrinologists, nutritionists and gastroenterologists, and a mental health team, including a psychiatrist…" (RCOG 2016, page 4).

[40] Gradae recommendation B is defined as "…A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+…" (RCOG, 2016, page 23). Classification of evidence level 2++ is defined as "…High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding,bias or chance and a high probability that the relationship is causal…"; level 1++ and 1+ include meta-analyses (*ibid*).

[41] *Hyperemesis gravidarum*

Synopsis of *Green-top Guideline No.69*

Give her one of several drugs for the present classed as antiemetics. If that does not work, try a cocktail of drugs. If that does not work, give her a drug or cocktail of drugs directly into blood or rectum, and why not corticosteroid. If that does not work, admit the patient and call the cavalry. And butcher, baker, *etc*.

Table 5. Acutherapy references mentioned in *Green-top Guideline No.69*, in order of appearance on page 12 (RCOG, 2016)			
#	**Reference**	**Remarks**	**ACURITE reference?**
1	(Caroline Smith, Crowther, and Beilby 2002a)	This RCT reported safety of acupuncture in NVP management. A guideline for needling practice is outlined.	No. Not published 2006 onwards.
2	(Helmreich, Shiao, and Dune 2006a)	RCT of 14 trials acutherapy for vomiting in general. I could not access this article's full text. Nor could I access full text for (Shiao and Dibble 2006) the first author of whom is co-author on Helmreich, Shiao, and Dune (2006), and which is published in the same volume of *Explore* journal.[42]	Barely *Yes* for the date. Not specific to NVP. So *No.*
3	(Belluomini et al. 1994)	I could not access full text for this article.	No. Not published 2006 onwards.
4	(Lee and Frazier 2011)	"…Investigators in 16 of 23 studies concluded acupressure was effective, primarily for the management of nausea and vomiting in patients during pregnancy and during chemotherapy…"	No. Not specific to NVP.

[42] As mentioned elsewhere, this articles appears not to be open access and neither is (Shiao and Dibble 2006) the first author of whom is co-author on Helmreich, Shiao, and Dune (2006), and which is published in the same volume of *Explore* journal.

NICE guideline NG201

GUIDELINE ANALSIS #2	
Published in	UK
Published by	National Institute for Health and Care Excellence
Publication name	*NICE guideline NG201*
Publication date	2021
Cited here as	(NICE 2022)
Link to pdf	Click here.
Link to website	Click here.

ACURITE for *NICE guideline NG201*		
Is acutherapy discussed in the text?		Yes
	With ACURITE references?	1 Yes (acupressure + mild NVP) 3 No (acupressure + severe NVP; acupuncture + mild NVP; acupuncture + severe NVP)
	With acutherapy method description?	No
Was acutherapy recommended?		consider for moderate to severe NVP
	With what grade?	n/a
Is therapy in the treatment algorithm?		Recommendation 1.4.6
Can this guideline be used to manage NVP with acutherapy?		No
Consistent regarding NVP acutherapy management?		No

Acutherapy in *NICE guideline NG201*

Recommendation 1.4.6 states: "…For pregnant women with moderate-to-severe nausea and vomiting: consider intravenous fluids, ideally on an outpatient basis (;) consider acupressure as an adjunct treatment…" (NICE 2022).

However, in *NICE guideline NG201, [R] Management of nausea and vomiting in pregnancy, Evidence reviews underpinning recommendations 1.4.1 to 1.4.7.* it is stated that: "…The recommendation to consider acupressure as a complementary therapy represents current practice and is usually administered as a self-administered therapy…" (NICE 2021b) page 65. It may not be assumed that intravenous fluids, considered along with acupressure *per* recommendation 1.4.6, is also to be self-administered, out- or inpatient.

The ACURITE 'acupressure for moderate to severe vomiting' reference used for the *NICE guideline NG201*

The reference used to generate recommendation 1.4.6 in NICE guideline 1.4.6 is (Adlan, Chooi, and Mat Adenan 2017). References used in the systematic review on which *NICE guideline NG201* is based can be accessed through links in Table 6. Rationale for the study chosen to generate recommendation 1.4.6 can be found in *Evidence reviews underpinning recommendations 1.4.1 to 1.4.6* see (NICE 2019a) for the pdf, (NICE 2021b) for the online. Notably on page 63 it states: "…One RCT from Malaysia (2017) reported that pregnant women with severe nausea and vomiting, who had received P6 acupressure in addition to standard care (IV fluids, IV metoclopramide and thiamine supplements) showed a clinically important difference on overall relief, nausea severity, and vomiting severity than those who had taken the placebo…" (NICE 2021b) page 63. This is important because (Adlan, Chooi, and Mat Adenan 2017) do not show data on a 'more severe' HG group *vs.* a less severe *severe* NVP group; the two groups are treatment and placebo, "…As it was unethical to withhold the standard treatment for severe HG…" (Adlan, Chooi, and Mat Adenan 2017) page 665. It is also difficult to deduce which group Adlan and others are referring to: only inpatient, inpatient then outpatient, or combinations of both. See also footnotes.

Table 6. Summary of acutherapy references used in *NICE guideline NG201,* click here to access (NICE 2021b)			
RCTs included in the NICE review	**Total**	**Of which were published 2011 onwards**	**ACURITE estimation**
For mild to moderate nausea and vomiting of pregnancy (click here for the relevant NICE data)			
Acupressure (R)CTs	7	4	Yes
Acupuncture (R)CTs	4	1	No
For moderate to severe nausea and vomiting (including hyperemesis gravidarum) (click here for NICE data)			
Acupressure (R)CTs	3	1	No
Acupuncture (R)CTs	1	nil	No

Why the ACURITE *Yes* result is not the same as

the reference used to generate NICE recommendation 1.4.6

The ACURITE *Yes* estimation is for references reviewed by NICE for NVP acutherapy for 'mild to moderate NVP'. Recommendation 1.4.6 is concerned with 'moderate to severe' NVP. Please note that neither acupuncture nor acupressure were deemed to be of any benefit for 'mild to moderate NVP' (NICE 2021b) page 60. This is also clearly emphasized in the text describing 'rationale and impact section on nausea and vomiting' (click here for link): "…An exception was for acupressure combined with standard care where the evidence showed benefits in relieving symptoms in women with moderate-to-severe nausea and vomiting in pregnancy, which was not shown for women with mild and moderate nausea and vomiting…" (NICE 2022).

In addition to (Adlan, Chooi, and Mat Adenan 2017), two other references informed the 'moderate to severe NVP' section of the *NICE guideline NG201*. These were not published 2011 onwards and so were marked ACURITE *No*. These are:

(i) (Heazell et al. 2006): all participants were inpatients who received "…cyclizine as a first-line agent, prochlorperazine as second-line agent, and metoclopramide, ondansetron, or phenothiazine…" (page 816). In other words, this RCT cannot support the statement made by NICE that "…women spend fewer days in hospital when given

acupressure in addition to standard treatment than a placebo and standard treatment…" since standard care is here defined as "…IV fluids, IV metoclopramide and thiamine supplements…" (NICE 2021b) page 63.[43]

(ii) (Habek et al. 2004): all participants were inpatients who may have received promethazine.

In addition to drugs not defined as 'standard care' by NICE being administered to participants of (Habek et al. 2004) and (Heazell et al. 2006), these two studies are further inapplicable within the *NICE guideline NG201* because IV fluids and drug(s) were administered to *inpatients*. Recommendation 1.4.6 states: "…consider intravenous fluids, ideally on an *outpatient* basis…" emphasis added, (NICE 2022). (Adlan, Chooi, and Mat Adenan 2017) is an ACURITE *Yes* reference and both (Habek et al. 2004) and (Heazell et al. 2006) are ACURITE *No*. ACURITE estimation for the NICE 'acupressure + moderate to severe NVP' was so an overall *No*.

In any case, (Heazell et al. 2006) and even less so (Habek et al. 2004) were *not* emphasized in the 'evidence underpinning' recommendation 1.4.6 (NICE 2021b) page 63.

Exclusion of studies and selection of study for recommendation 1.4.6 'acupressure for moderate to severe NVP'

in *NICE guideline NG201*

For a list of studies excluded from data underpinning the *NICE guideline NG201,* see Appendix K of (NICE 2021b). This list includes (Matthews et al. 2015) because, it is stated: "…References checked, no additional studies were identified…".

Of course, studies may have been excluded for reasons of high threshold for quality evidence, for example: "…One RCT from Croatia (2004) reported a clinically important difference favouring P6 acupuncture over placebo for pregnant women on the number of women with relief from symptoms. However, since this was the only evidence found for this intervention and it was of a low quality, the committee did not

[43] It is interesting to note that the definition of 'standard care' given on page 63 of (NICE 2021b) is more or less identical to that in (Adlan, Chooi, and Mat Adenan 2017); on page 665 of the latter it states: "…As it was unethical to withhold the standard treatment for severe HG, both groups were administered intravenous fluid and regular intravenous metoclopramide and thiamine supplements during inpatient admission. The total dose and amount of fluid infusion were therefore not considered as outcome parameters…". This, at least, further confuses just how much of what which participant got. When.

recommend acupuncture for severe nausea and vomiting…in pregnancy…" (NICE 2021a) page 63.[44]

Eligibility criteria may have already pre-excluded many studies, see Appendix A of (NICE 2021b) click here for the pdf, which, in turn, mentions other potential criteria for pre-exclusion such as *Developing NICE guidelines: the manual.*

Indeed, 43 out of a total of 184 references were selected as evidence underpinning NVP recommendations in *NICE guideline NG201*, and 141 excluded (NICE 2021a) page 79. Nevertheless, that (Adlan, Chooi, and Mat Adenan 2017) only is used to inform NICE on acutherapy in NVP did not appear commensurate.

Synopsis of *NICE guideline NG201*

Try ginger and reassurance. If that does not work, see if she had (in an earlier pregnancy) *preferred* an antiemetic, and if she chooses to take drugs, *offer* an antiemetic. If it gets worse, treat her as an outpatient with IV fluids and acupressure. If she does not respond as an outpatient, consider admission to hospital.

[44] One may argue that (Adlan, Chooi, and Mat Adenan 2017) was also the only evidence showing benefit of acupressure for moderate to severe NVP, and was also of low quality. Nevertheless, it made it through all the way up to recommendation 1.4.6 in (NICE 2022). Alone.

Practice Bulletin No.189

GUIDELINE ANALSIS #3	
Published in	US
Published by	American College of Obstetricians and Gynecologists
Publication name	*Practice Bulletin No.189*
Publication date	2018
Cited here as	(Erick, Cox, and Mogensen 2018)
Link to pdf	Not open access
Link to website	Click here.

ACURITE for *Practice Bulletin No.189*		
Is acupuncture discussed in the text?		Yes
	With ACURITE references?	Yes
	With acupuncture method description?	P6 is described, wristbands are recommended
Was acupuncture recommended?		Wristbands
	With what grade?	Emphasizes no benefit
Is acupuncture in the treatment algorithm?		Yes but not summary
Can this guideline be used to manage NVP with acutherapy?		Yes?
Consistent regarding NVP acutherapy management?		No

Acupuncture in *Practice Bulletin No.189*

The authors were inconclusive about putative efficacy of acupuncture in management of NVP on page e19 (Erick, Cox, and Mogensen 2018). Three references are mentioned namely: (Roscoe and Matteson 2002) which is a (very) brief review of acupressure and acustimulation *wristbands*; and (Matthews et al. 2015) and (McParlin et al. 2016) discussed elsewhere.

To "…Consider P6 acupressure with wrist bands…" is a 'first line therapy' in the treatment algorithm on page e20, along with folic acid-only supplements and ginger (Erick, Cox, and Mogensen 2018). Yet no mention of acupressure is made in the 'summary of recommendations' on page e25. Ginger is mentioned in the 'summary of recommendations' of *Practice Bulletin No.189.*

Management of NVP in the *Practice Bulletin No.189* treatment algorithm and synopsis

Non-pharmacologic options in the treatment algorithm are folic acid-only supplements, ginger, and acupressure. Subsequently, the algorithm moves onto pharmacologic options starting with pyridoxine with or without doxylamine. Protocols are described in detail and comprehensively.

Pregnancy Care 2020 Edition

GUIDELINE ANALSIS #4	
Published in	Australia
Published by	Australian Government Department of Health
Publication name	*Pregnancy Care 2020 Edition*
Publication date	2020
Cited here as	(AGDoH 2020)
Link to pdf	Click here.
Link to website	Click here.

ACURITE for *Pregnancy Care 2020 Edition*		
Is acupuncture discussed in the text?		Yes
	With ACURITE references?	No
	With acupuncture method description?	No
Was acupuncture recommended?		No
Is acupuncture in the treatment algorithm?		No
Can this guideline be used to manage NVP with acupuncture?		No
Consistent regarding NVP acupuncture management?		No

Role of acupuncture in *Pregnancy Care 2020 Edition*

In discussing a role for acutherapy in the management of NVP, the *Pregnancy Care 2020 Edition* refers to (Matthews et al. 2010) and not (Matthews et al. 2015) as the 'highest quality study' (AGDoH 2020). All references mentioned for acutherapy and NVP are discussed in Table 7. In addition to NVP, acupuncture is discussed as a therapy option for reflux in pregnancy, pelvic pain, and external cephalic version or breech presentation in the *Pregnancy Care 2020 Edition* (AGDoH 2020).

Synopsis of *Pregnancy Care 2020 Edition* NVP practice summary

The *Pregnancy Care 2020 Edition* NVP management 'practice summary' is aimed at "…midwife; GP; obstetrician; Aboriginal and Torres Strait Islander health worker; multicultural health worker; dietitian; pharmacist…" (AGDoH 2020) page 295. NVP is to be managed by: (i) 'informing women' that NVP is not harmful, common, not just in the morning, and likely to go away by week 16; (ii) 'advice and tips' including acknowledging that NVP can affect well-being and avoid fatty food; and (iii) 'discussing with the woman who asks' non-pharmacologic as well as pharmacologic treatment of NVP.[45]

Role of acupuncture and NVP in publications related to *Pregnancy Care 2020 Edition*

In *Pregnancy Care – Linking evidence to recommendations (revised April 2019)* and found here), under "…Nausea and vomiting (reviewed 2010)…" is the "…NICE recommendation…" informing women that NVP will go away by week 16 *or 20* and "…If a woman requests or would like to consider treatment, the following interventions appear to be effective in reducing symptoms: non-pharmacological: ginger, P6 (wrist) acupressure pharmacological: antihistamines…" (AGDoH 2018b) page 63.[46] It is reported that Medline, Embase, and Google Scholar were searched in 2010 to extract these data (*ibid*).[47]

[45] The text reads: "…**Discuss non-pharmacological and pharmacological treatments:** If the woman asks about treatments for nausea and vomiting, suggest interventions that may help and are thought to be safe, beginning with non-pharmacological approaches. The safety and effectiveness of antiemetics should be discussed with women with more severe symptoms who choose to consider medication…" (AGDoH 2020) *sic*, emphasis in the original, page 295.

[46] For contrast, see actual NICE recommendations.

[47] This is important. In *Pregnancy Care - Administrative report (revised April 2019)* found here, "…Systematic literature search and review undertaken to:…update evidence tables (where new evidence exists)…" (AGDoH 2018a) page 7. Needless to say, this administrative requirement is equally lacking in, for example, references to acupuncture used in *Pregnancy Care 2020 Edition* and summarized in Table x.

In *Pregnancy Care – Short-form guideline (revised April 2019)* and found here, acupuncture is recommended for pelvic girdle pain (AGDoH 2018c) page 20. For NVP, 'informing the woman' that it will go away by 16 *to 20* weeks is recommended (NICE is not mentioned). Also reducing iron supplements.

Common Conditions During Pregnancy found here (AGDoH 2019) gives the 'practice summary' in *Pregnancy Care 2020 Edition* (AGDoH 2020) discussed above and which does not mention acutherapy.

Synopsis of NVP management in *Pregnancy Care 2020 Edition* and related publications

Tell the woman it will go away in four or five months. If the woman does not go away, you may have to tell her something else, exactly what is not clear.

Table 7. Acupuncture references mentioned in *Pregnancy Care 2020 Edition* (AGDoH 2020) in order of appearance pages 293-4			
#	**Reference**	**Remarks**	**Is this an ACURITE reference?**
1	(Matthews et al. 2010)	Not (Matthews et al. 2015). In other words, the formerly relevant Cochrane Systematic Review.	Not unless the more recent and relevant Cochrane review is suspect.
2	(Murphy 1998)	This systematic review of alternative therapies in the management of NVP recommends acupressure namely, as well as ginger and pyridoxine.	No. Not published after 2006.
3	(Vickers 1996)	This is a systematic review of P6 stimulation for 'nausea and/or vomiting associated with chemotherapy, pregnancy, or surgery' and strongly recommends it.	No. Not published after 2006.
4	(Caroline Smith et al. 2000)	As this more general review article was referred to in the context of safety, it would be reasonable to assume that the more recent publication by those authors (Caroline Smith, Crowther, and Beilby 2002a) and which clearly discusses safety of acupuncture in pregnancy, was rather intended.	No. Probably erratic.

SOMANZ 2019

GUIDELINE ANALSIS #5	
Published in	Australia and New Zealand
Published by	Society of Obstetric Medicine of Australia and New Zealand
Publication name	*SOMANZ 2019*
Publication date	2019
Cited here as	(Lowe et al. 2019b) and (Lowe et al. 2019a)
Link to pdf(a)	Click here.
Link to pdf(b)	Click here.
Link to website	Click here.

ACURITE for *SOMANZ 2019*		
Is acutherapy discussed in the text?		Yes
	With ACURITE references?	2 Yes, 2 No
	With acupuncture method description?	No
Was acutherapy recommended?		No (strongly)
Is acupuncture in the treatment algorithm?		No
Can this guideline be used to manage NVP with acupuncture?		No
Consistent regarding NVP acupuncture management?		Yes

Acutherapy in *SOMANZ 2019*

Unlike the *NICE guideline NG201*, acutherapy in (Lowe et al. 2019b), the main text of *SOMANZ 2019* is not concerned with severe NVP.

The SOMANZ 2019 states: "…Very few studies are available in English language journals of the use of traditional acupuncture for the treatment of NVP. Only two trials compared acupuncture to sham or placebo treatment, neither found clinically significant improvement in symptoms…" and cite (Knight et al. 2001) and (C Smith and Crowther 2002). But (C Smith and Crowther 2002) "…explore[d] some aspects of the placebo response…" and sought "…to unravel and understand the benefits that women experience from being allocated to the sham acupuncture study group…" (C Smith and Crowther 2002) page 216. Surely, the authors of *SOMANZ 2019* had meant to rather cite (Caroline Smith, Crowther, and Beilby 2002a) in this context? That this is indeed so is shown in the sentence immediately following the citation of (Knight et al. 2001) and (C Smith and Crowther 2002) in *SOMANZ 2019*: "…No serious adverse outcomes from the use of acupuncture were reported…" (Lowe et al. 2019b) page 17. Clearly, the apparent must-reference for acutherapy safety in NVP, (Caroline Smith, Crowther, and Beilby 2002a), was implied. In any case, none of these references were published 2009 onwards, and so are ACURITE *No*.

After bemoaning the paucity of available studies in English on acutherapy for NVP, (Lowe et al. 2019b) later cite (Matthews et al. 2015) which is ACURITE *Yes*.

The third and final reference for acutherapy in *SOMANZ 2019* is (Adlan, Chooi, and Mat Adenan 2017), the reference used to generate recommendation 1.4.6 in *NICE guideline NG201*, and which is ACURITE *Yes*.

Apparently the authors of *SOMANZ 2019* (Lowe et al. 2019b) did not appreciate the value of (Adlan, Chooi, and Mat Adenan 2017) as much as the authors of *NICE guideline NG201*: "…Interestingly a greater percentage of the placebo group [in the (Adlan, Chooi, and Mat Adenan 2017) study] were satisfied with their treatment (85%) than the treatment group (72%, $p < 0.8$)…" (Lowe et al. 2019b) page 18.

Synopsis of acutherapy in *SOMANZ 2019*

The *SOMANZ 2019 Executive Summary* states: "…Although acupuncture, acupressure and hypnosis are safe, they have shown no clinically significant effect for NVP or HG…" (Lowe et al. 2019a) page 9 . This recommendation was graded 'EBR' or "…Where sufficient evidence was available…" (Lowe et al. 2019a) page 3.[48]

The treatment algorithm for NVP and HG is given on page 60 of the *SOMANZ 2019* main text (Lowe et al. 2019a) and acutherapy is not mentioned. The treatment algorithm is comprehensive. Briefly, antiemetics and laxatives would be administered early on in a case of mild to moderate NVP, along with diet changes, ginger, folate-only and pyridoxine regimes

[48] The other two possible recommendations are 'CBR' or "…Where there was insufficient evidence, the expert guideline development group made clinical consensus recommendations…"; and 'CPP' or "…Important implementation and other issues (such as safety, side effects or risks) arose from discussion of evidence based or clinical consensus recommendations…" (Lowe et al. 2019a) page 3.

SOG-C

GUIDELINE ANALSIS #6	
Published in	Canada
Published by	Society of Obstetricians and Gynecologists of Canada
	Public Health Agency of Canada
Name	*SOG-C*
Publication date	2016 and 2020
Cited here as	(Campbell et al. 2016) and (Wagner et al. 2020)
Link to pdf and website	(Campbell et al. 2016) is paywalled. For (Wagner et al. 2020) click here or here.

ACURITE for *SOG-C*		
Is acutherapy discussed in the text?		Yes
	With ACURITE references?	No
	With acupuncture method description?	Yes
Was acupuncture recommended?		Yes
Is acupuncture in the treatment algorithm?		No
Can this guideline be used to manage NVP with acupuncture?		Yes
Consistent regarding NVP acupuncture management?		Yes

Acutherapy in the *SOG-C*

In *Canada Public Agency of Health Care During Pregnancy (Chapter 3)*, section 5 *First Trimester Care*, section 5.2 *Nausea and Vomiting*, there is no mention of acutherapy (Wagner et al. 2020) pages 32-33. The reader is referred to (Campbell et al. 2016) for further reading and treatment algorithm. However, acupuncture is mentioned once as one of several "…complementary methods of inducing labour such as castor oil, intercourse,…or breast stimulation…" (Wagner et al. 2020) page 50.

Moving on to (Campbell et al. 2016). ACURITE analysis for acutherapy references are in Table 8. The total ACURITE score is *No.*

P6 is described and even illustrated on page 1131.

"…Acupressure may have some value in the management of nausea and vomiting of pregnancy…" and this recommendation is grade (I-B) or "…I: Evidence obtained from at least one properly randomized controlled trial…" and so "…There is fair evidence to recommend the clinical preventive action…" (Campbell et al. 2016) pages 1128 and 1130.

Treatment algorithm and synopsis

Acutherapy is not in the treatment algorithm, but neither are other non-pharmacologic treatments including ginger, psychotherapy, as well as diet and lifestyle.

The treatment algorithm is comprehensive for pharmacological treatment. Briefly, it starts with pyridoxine or doxylamine, adds dimenhydrinate, followed by metoclopramide, chlorpromazine, and so on.

Table 8. Analysis of references cited in (Campbell et al. 2016)			
Reference	**Context in which reference is used in (Campbell et al. 2016), quoted below *verbatim* from page 1130**	**What the reference is actually about**	**ACURITE reference?**
(Streitberger, Ezzo, and Schneider 2006)	"…There is good evidence to support the use of acupuncture for nausea and vomiting…"	This article 'overviews' acutherapy for nausea and vomiting in general including motion sickness. And it states: "…For pregnancy-related nausea and vomiting, results were mixed…"	Barely *Yes* for the date and *No* for the topic. So *No*
(Neutel and Johansen 2000)	"…However, there is insufficient data for this intervention in pregnant women…"	This reference is titled *Variation in rates of hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada.* It is very strange.	*No* for the date and *No* again for the topic.
(Matthews et al. 2015)	"…Acupressure is affordable, is easy to self-administer, appears safe, and may be beneficial in reducing NVP for some women…"	There might be a typo in the (Wagner et al. 2020) references (reference number 14) for this authoritative piece, the date there is 2014.	Yes

Reference	Context in which reference is used in (Campbell et al. 2016), quoted below *verbatim* from page 1130	What the reference is actually about	ACURITE reference?
(Lee and Frazier 2011)	"…Acupressure applied to P6 has been demonstrated to reduce nausea and episodes of vomiting for women with NVP, although there are limitations to these findings…"	This is concerned with chemotherapy induced nausea and vomiting as well as NVP.	No
(Roscoe and Matteson 2002)		This is concerned with NVP as well as other nausea and vomiting.	*No* for the date and *No* again for the topic.
(Shin, Song, and Seo 2007)		This reports that P6 acupressure is useful in HG.	Yes
TOTAL ACURITE ESTIMATE: 4 *No* and 2 *Yes*. So *No*			

WHO Recommendations

GUIDELINE ANALSIS #7	
Published in	International
Published by	United Nations World Health Organization
Name	*WHO Recommendations*
Publication date	2016
Cited here as	(WHO 2016)
Link to pdf	Click here.

ACURITE for *WHO RECOMMENDATIONS*		
Is acutherapy discussed in the text?		Yes
	With ACURITE reference?	Yes
	With acupuncture method description?	No
Was acupuncture recommended?		Yes
Is acupuncture in the treatment algorithm?		Yes
Can this guideline be used to manage NVP with acutherapy?		Yes
Consistent regarding NVP acutherapy management?		No

Acutherapy reference for NVP in the *WHO Recommendations*

On page 75 of *WHO recommendations on antenatal care for a positive pregnancy experience*, under 'effects for interventions for NVP', it is stated: "…The evidence on the effects of various interventions for nausea and vomiting in pregnancy was derived from a Cochrane systematic review…" and Matthews et al. (2015) is cited (WHO 2016). It goes on to say: "…Alternative therapies and non-pharmacological agents evaluated included acupuncture, acupressure, vitamin B6, ginger, chamomile, mint oil and lemon oil. Pharmacological agents included antihistamines, phenothiazines, dopamine-receptor antagonists and serotonin 5-HT3 receptor antagonists. Due to heterogeneity among the types of interventions and reporting of outcomes, reviewers were seldom able to pool data. The primary outcome of all interventions was maternal relief from symptoms (usually measured using the Rhodes Index), and perinatal outcomes relevant to this guideline were rarely reported…" (WHO 2016, page 75).

***WHO Recommendations* did not pool data**

Under 'Acupuncture and acupressure versus placebo or no treatment', the authors briefly describe the features of eight of the (R)CTs analysed by Matthews et al. (2016), see Table 1. And then conclude: "…Low-certainty evidence suggests that P6 acupressure may reduce nausea symptom scores…and reduce the number of vomiting episodes…Low-certainty evidence…suggests that auricular acupressure may also reduce nausea symptom scores…as may traditional Chinese acupuncture…Low-certainty evidence suggests that P6 acupuncture may make little or no difference to mean nausea scores compared with P6 placebo acupuncture…" (WHO 2016, pages 75 and 76).

Under 'Additional considerations', the authors summarise "…Low-certainty evidence [from studies analysed by Matthews et al. 2015 see Table 1.] from single studies comparing different non-pharmacological interventions with each other – namely acupuncture plus vitamin B6 versus P6 acupuncture plus placebo traditional acupuncture and P6 acupuncture…ginger…vitamin B6…" *etc.* and conclude: "…suggests there may be little or no difference in effects on relief of nausea symptoms….".

Acutherapy for NVP in *WHO Recommendations*

Under "Resources…Acupuncture requires professional training and skills and is probably associated with higher costs…" and under "Feasibility… A lack of suitably trained staff may limit feasibility of

certain interventions (high confidence in the evidence)…" (WHO 2016 pages 74 to 77), and (Downe et al. 2016a) is cited.[49]

Under "Acceptability…Qualitative evidence…suggests that women may be more likely to turn to traditional healers, herbal remedies or traditional birth attendants (TBAs) to treat these symptoms (moderate confidence in the evidence) [(Downe et al. 2016a) citation]…In addition, evidence from a diverse range of settings indicates that while women generally appreciate the interventions and information provided during antenatal visits, they are less likely to engage with services if their beliefs, traditions and socioeconomic circumstances are ignored or overlooked by health-care providers and/or policy-makers (high confidence in the evidence). This may be particularly pertinent for acupuncture or acupressure, which may be culturally alien and/or poorly understood in certain contexts…" (WHO 2016, pages 76 and 77).

Under "…Women's Values…A scoping review of what women want from ANC and what outcomes they value informed the ANC guideline [(Downe et al. 2016b) is cited]…Evidence showed that women from high-, medium- and low-resource settings valued having a positive pregnancy experience. This included woman-centred advice and treatment for common physiological symptoms (high confidence in the evidence)…this also included support and respect for women's use of alternative or traditional approaches to the diagnosis and treatment of common pregnancy-related symptoms (moderate confidence in the evidence)…".

Nevertheless "…RECOMMENDATION D.1 [Interventions for NVP]: Ginger, chamomile, vitamin B6 and/or acupuncture are recommended for the relief of nausea in early pregnancy, based on a woman's preferences and available options. (Recommended)…In the absence of

[49] Reference 13 in WHO (2016): "…Downe S, Finlayson K, Tunçalp Ö, Gülmezoglu AM. What matters to women: a scoping review to identify the processes and outcomes of antenatal care provision that are important to healthy pregnant women. BJOG. 2016;123(4):529–39. doi:10.1111/1471-0528.13819…". This is cited in the present work as (Downe et al. 2016b). Reference 22 in WHO (2016): "…Downe S, Finlayson K, Tunçalp Ö, Gülmezoglu AM. Factors that influence the use of routine antenatal services by pregnant women: qualitative evidence synthesis. Cochrane Database Syst Rev. 2016;(10):CD012392…". This is cited in the present work as (Downe et al. 2016a). Reference 45 in WHO (2016): "…Downe S, Finlayson K, Tunçalp Ö, Gülmezoglu AM. Factors that influence the provision of good quality routine antenatal care services by health staff: a qualitative evidence synthesis. Cochrane Database Syst Rev. 2016 (in press)…". This is also cited in the present work as (Downe et al. 2016a) because references 22 and 45 in WHO (2016) appear to be the same. The most recent relevant publication by those authors is (Downe et al. 2019).

stronger evidence…these non-pharmacological options are unlikely to have harmful effects on mother and baby…Women should be informed that symptoms of nausea and vomiting usually resolve in the second half of pregnancy…Pharmacological treatments for nausea and vomiting, such as doxylamine and metoclopramide, should be reserved for those pregnant women experiencing distressing symptoms that are not relieved by non-pharmacological options, under the supervision of a medical doctor…" (WHO 2016, page 74).

And under 'Executive summary – interventions for common physiological symptoms – nausea and vomiting': "…Ginger, chamomile, vitamin B6 and/or acupuncture are recommended for the relief of nausea in early pregnancy, based on a woman's preferences and available options…." (WHO 2016, page xv).

Acutherapy for other conditions in *WHO Recommendations*

Acutherapy is discussed for low back and pelvic pain, and heart burn. More or less the same text quoted above for NVP acutherapy under 'resources', 'feasibility', and 'acceptability' is repeated for heart burn. For low back and pelvic pain it is emphasized: "…Physiotherapy and acupuncture require specialist training and are therefore likely to be more resource intensive…In addition, where there are likely to be additional costs associated with treatment or where the treatment may be unavailable (because of resource constraints), women are less likely to engage with health services (high confidence in the evidence)…A lack of resources may limit the offer of treatment for this condition (high confidence in the evidence) [(Downe et al. 2016a) citation]…." (WHO 2016, page 81).

Synopsis of acutherapy for NVP in *WHO Recommendations*

DO NOT prescribe antiemetics UNLESS you've tried ginger, chamomile, pyridoxine, and acutherapy, AND you are a medical doctor. But acupuncture is expensive and rare, and so not feasible, and acupuncture is also alien and poorly understood, and so not acceptable.

***Green-top guideline No.69* 2016**

In *Green-top Guideline No.69*, NVP is to be diagnosed by exclusion of other causes. Such a gate keeping function (Lewin 1947) may exclude many health care professionals from using the Guideline.[50] The treatment algorithm given is less of a practical-guideline and more of a thought-guideline for the highly qualified and experienced. However, if the Royal College of Obstetricians & Gynaecologists (UK) is addressing experienced fellow(es) and colleagues in the Guideline, would it not be safe to assume that the most authoritative (and hopefully recent) references are cited? So that said experienced fellow(es) and colleagues will have immediate (and hopefully open) access to the most up-to-date and definitive references on a topic, say acutherapy for the management of NVP. Instead, Matthews et al. (2015) is not cited. Not even Matthews et al. (2010) is cited in the relevant text. Not even the older relevant Cochrane review (Jewell and Young 2003) is cited. A reason why any one of the four references mentioned by the *Green-top guideline NG201* were cited at all by the developers when discussing acutherapy management of NVP appears mysterious (see Table 5.). It is tedious to go into details one by one, even if there are only four of them. In any case, we can only speculate why the developers at the Royal College of Obstetricians & Gynaecologists (UK) chose to cite those four references, and absurdly.[51]

And none of these four references is Matthews et al. (2015). None of these four references is even Matthews et al. (2010), or the earlier Cochrane review (Jewell and Young 2003). One should rather consult with a 2011 article in *Journal of Pain and Symptom Management*.

If the Cochrane reviews are not OK, we need to be told. Did the Royal College of Obstetricians & Gynaecologists (UK) *shun* Matthews *et al.* (2015)? Or even Matthews et al. (2010)? And (Jewell and Young 2003)?

[50] A gate here is "…the constellation of the forces before and after the gate region is decisively different in such a way that the passing or not passing of the unit through the whole channel depends to a high degree upon what happens in the gate region…This holds…for the travelling of a news item through certain communication channels in a group…"; a gate keeper is: "…Gate sections are governed either by impartial rulers or by 'gate keepers'…" (Lewin 1947, page 145).

[51] Absurdly here refers to a speculation, not the reason(s) the developers had for citing those four references listed in Table 5. though it may appear otherwise.

***NICE guideline NG201* 2022**

Exclusion of all studies but one

Perhaps the Royal College of Obstetricians & Gynaecologists (UK) *did* indeed shun Matthews et al. (2015) as well as Matthews et al. (2010). It might be safe to assume that even O'Donnell et al. (2016) was also shunned by the developers of the *NICE guideline NG201* and which, needless to say, rely on guidelines from the Royal College of Obstetricians & Gynaecologists (UK). This is odd because if data from Matthews and others at Cochrane is not OK, surely data from O'Donnell and others at the National Institute for Health Research (UK) *is* OK?

In any case, the developers at NICE set out to do what Matthews and O'Donnell and many others had done (albeit differently): systematically review all (R)CTs they could find for acutherapy and NVP management. And to be thorough, NICE developers did take a look at everything else they found on the way, including other systematic reviews and books of the same. They were transparent about how they did the systematic review and this is commendable.

What is not commendable is that the developers of *NICE guideline NG201* proceeded to exclude *all* studies until only *one* was left. Some of these studies *Excluded Before Analysis* and all those *Excluded After Analysis* are labelled in the present work as *EBA and EAA*, respectively. In fact, the developers excluded about thirty (R)CTs, fifteen or more systematic reviews including Matthews et al. (2015) *and* (2010), O'Donnell (2016), and several books discussing acutherapy in NVP management. Always, the developers, in the NICE Appendix K, told us that references were cross-checked with this particular review or book, and if they had found any additional references, the developers tell us the number. A total of thirteen (R)CTs made it through for analysis by NICE, see Table 6.

Since one study was selected for generation of recommendation 1.4.6 (*i.e.* after analysis, and that reference is (Adlan, Chooi, and Mat Adenan 2017), the exclusion process is meaningless.

Meaning of recommendation 1.4.6

NICE developers recommend acupressure for moderate to severe NVP and not for mild to moderate NVP as recently noted by (Savona-Ventura and Mahmood 2022). A reasonable physiological view may hold that this benign, almost certainly harmless, and mechanistically complex intervention would be more appropriate for management early in the presentation of NVP, in other words with mild to moderate NVP. But NICE recommend acupressure for moderate to severe NVP. Of course, this is something the patient should do on her own, it is 'self-administered', we are told, in case there was any doubt.

But the recommendation for acutherapy comes along with IV fluids, preferably as an outpatient, both are recommendation 1.4.6. Do we poke

the patient with our finger in the same arm in which we poke the cannula, for the IV fluids? Or the contralateral arm? No, wait, she will poke her own arm when she goes home. Anyways, acupressure for moderate to severe NVP is an *adjunct* therapy, to be considered, along with IV fluid standard care à la (Adlan, Chooi, and Mat Adenan 2017) see fotnote 27. As an outpatient please; consideration to admit mum as an inpatient is to be done only if she is very poorly, and outpatient management ('IV fluid standard care') + self-administered acupressure has failed to improve nausea and vomiting, perhaps several times.

This meaninglessness results from the following: that the authors of the reference used for generation of NICE recommendation 1.4.6 (Adlan, Chooi, and Mat Adenan 2017) thought it was *ethical* to treat patients suffering from mild NVP the same way they treated patients with severe NVP. In other words, that participation in a clinical trial (of sorts), as opposed to diagnosis, is an indication for treatment.

(Adlan, Chooi, and Mat Adenan 2017) mixed the inpatient with the outpatient, with the inpatient who became an outpatient, with the inpatient who stayed as an inpatient. NICE developers were more sure about this: treat her as an outpatient please.

Let her choose to take antiemetics

A user of the *NICE guideline NG201* is to check if the multigravida had previously *preferred* antiemetics. And for mutli- and primigravida *who choose a pharmacological treatment*, the user is to *offer* an antiemetic. A link to a table informs user of the advantages and disadvantages of stuff which acts on histamine, dopamine, serotonin, all kinds of stuff, to discuss with mum. Another link takes the user to *shared decision making*. May it be safe to extrapolate that the user, the health professional for whose benefit *NICE guideline NG201* was developed, as well as all those outside the UK who look to this definitive source for guidance, would have liked to have a decision made for them, and so for mum? Because mum feels bad, she may have tried this or that, and nothing seems to be working, and it would be great if someone who's done a lot of work excluding evidence could guide us.

NICE's answer is clear and firm and not so nice: the decision to take drugs lies with *the woman.*

Pregnancy Care 2020 Edition

The Australian Government Department of Health told us that *Pregnancy Care 2020 Edition* has to be updated regularly, and told us that the references were checked to be the most up-to-date. And then told us that the *highest* reference of a grand total of four to consider with regards acutherapy for management of NVP is Matthews et al. 2010. Not 2015. Note this is the *2020 Edition*.

The health professional or guideline user is told to wait until the woman *asks* if there is anything to help with NVP. And then to tell the woman to choose to take drugs.

Under 'Resources' for NVP in *Pregnancy Care 2020 Edition*, there is only one reference cited click here. This one reference, or resource despite allegations of plurality, is (Arsenault and Lane 2002) - which, the publisher is very quick to inform us, is RETIRED and should *not* be consulted for any reason other than historical. Fortunately, the user of *Pregnancy Care 2020 Edition*, is *not* taken to Arsenault and Lane (2002) by the link provided in the online *Pregnancy Care 2020 Edition*. The user is taken to (Campbell et al. 2016), which is the more recent guideline from Society of Obstetricians and Gynecologists of Canada, analysed above along with (Wagner et al. 2020). Well anyways, Campbell *et al.* (2016) and Arsenault and Lane (2002) read identically in parts (the text is more or less identical in parts), but of course there are important differences, obviously, or the publisher would not make us declare never to use Arsenault and Lane (2002) for any purpose other than historical. And anyways neither Campbell et al. (2016) nor Arsenault and Lane (2002 RETIRED) are open access. So the user is kind of told to find resource(s) for him- or herself. The various handouts for various users that come along and around the *Pregnancy Care* as well as the *2020 Edition* address mum (through the user) in what I thought was a most rude manner. And basically the management of NVP is to tell mum to bugger off, so we should not be surprised that user, in addition to mum, may also check the resource (in the single plurality, and assuming user literacy, of course) and also bugger off.

And it told the user to withhold information from mum which may help until asked for it – what is the confidence level in that recommendation?

The point to make here before moving on is that confidence was lost in what one was told by *Pregnancy Care 2020 Edition* quickly and thoroughly.

Active science and methods *vs.* retired science and methods

The resource furnished by the Australian Government Department of Health so the user may not check because it is RETIRED, Arsenault and Lane (2002) write: "…Though there are no theoretical concerns about the safety of acupressure in pregnancy, efficacy of P6 acupressure is difficult to prove because it is impossible to perform a true double-blind trial compared with no intervention. *Nonetheless*, non-blinded RCTs have demonstrated a decrease in 'persisting nausea' by at least 50%... [and cite Jewell and Young (2003)]…" (emphasis added, Aresenault and Lane 2002, page 819).

A feeling of disbelief which may be communicated from reading this paragraph is well reflected in the text from Vickers (1996), quoted in the present work in footnotes. What, authors have been asking, is it exactly that you want to see?

WHO – circling back to Matthews (2015) and O'Donnell (2016)

There is only one source of evidence for acutherapy management of NVP in (WHO 2016) and that is Matthews et al. (2015). Which is fine, it is what Cochrane are there for, to do that EBM work. What the authors of (WHO 2016) appeared to find *not* fine is throwing in numbers from studies together.

So the authors of (WHO 2016) took the references from Matthews et al. (2015) one by one, described the findings, and stated how confident or not they were regarding this reference, this piece of evidence.

Kind of like what O'Donnell et al. (2016) eventually ended up doing.[52] WHO (2016) tell us the evidence on acutherapy management of NVP from (R)CTs is what it is. But acutherapy is expensive and needs trained specialists and it's not feasible. And acutherapy is *alien.* And poorly understood.

Alien acutherapy

The least flattering reference to acutherapy in all the guidelines analysed has to be the one in (Wagner et al. 2020), the one about alternative methods for inducing labour. How does a healthcare professional suggest to mum to have a shag, some castor oil, breasts fondled, and acupuncture? Can those methods be combined? In series or perhaps even in parallel?

The discourse on acutherapy in (WHO 2016) is concerning. The authors appear to definitely not want to hand out pills. So we must do everything we can to help without pills, and the evidence about acutherapy for NVP is what it is. And what about acutherapy for heartburn and low back and pelvic pain? Not terribly enthusiastic about heartburn. For low back and pelvic pain, the authors seem to appreciate the therapeutic potential of acutherapy.

But for all of NVP, heartburn, and low back and pelvic pain: acutherapy requires trained specialists and rare resources which are expensive and so it is not feasible; and it may be perceived as alien and so it is unacceptable. The references used to support these arguments are in footnotes of the present work. Briefly, (Downe et al. 2016a) is the relevant Cochrane protocol, and so is an irrelevant reference, because there are no findings, unless you want to make sure that the findings, which would come in 2019, will be solid. (Downe et al. 2016b) finds that "…A positive pregnancy experience matters across all cultural and

[52] "… Data were therefore summarized narratively and prioritized to emphasize the highest quality of evidence, defined as randomized clinical trials with a low risk of bias…" under Methods in (McParlin et al. 2016) page 1393. It is interesting to note the NICE developers excluded narrative reviews offhand, see Appendix K of the NICE Guideline.

sociodemographic contexts…". Later (Downe et al. 2019) finds that "…women use antenatal care if they find it is a positive experience that fits with their beliefs and values, is easy for them to access, affordable, and treats them as an individual. …".

Of course, WHO (2016) did not have access to Downe et al. (2019). Nevertheless, the difficulty in fitting earlier work by Downe and others into the *WHO Recommendations* specific to acutherapy is further compounded by the following: Are the authors of *WHO Recommendations* aware that some of the majority of people in the world, in say China, Malaysia, Indonesia, Japan, and California, may perceive acutherapy as ineffectual or even quackery, but certainly not *alien*?

SOMANZ 2019

The Society of Obstetric Medicine of Australia and New Zealand, represented by Lowe et al. (2019a/b), did not like acutherapy. One cannot blame them. Look at what they wrote about (Adlan, Chooi, and Mat Adenan 2017). Maybe they thought it was alien.

Practice Bulletin No.189

Matthews et al. (2015) and McParlin et al 2016 (which is the O'Donnell et al. (2016) study) are cited, and another one for wrist bands, check with your local pharmacy.

Discussion

A role for NVP management with acutherapy in EBM is overall unclear. In my opinion, an adjective which may more or less describe acutherapy management of NVP in EBM is ‘miserable’.

Some national guidelines tell us to try acutherapy or wristbands for NVP, some say don’t bother, some tell us we *must* try acutherapy for NVP, and let us leave NICE to one side for the moment.

Well, obviously. The relevant EBM is in Matthews et al. (2010) and (2015), O’Donnell et al. (2016), and the evidence in there comes from (R)CTs . Which we simply cannot see, mostly, because the (R)CT in question is obsolete, or behind a paywall, or just an abstract. And when we *can* see the full text (R)CT cited by Matthews et al. (2015) and/or O’Donnell et al. (2016) it much more often than not looks like…well.

Vomit really.[53]

[53] This has word has regrettable connotations in general and in particular, so garbage will be used.

So garbage in garbage out? The garbage is nuanced. Do you put the garbage in the blender? Or do you process the garbage one by one? Or do you take the items of garbage that someone else chose to put in a blender, and then process it one by one?

The prize for collecting the most items of garbage goes to NICE, hands down. And then they threw all that garbage out except thirteen pieces. And then they threw ten of those away (mild to moderate NVP). And then kind of smuggled two of the remaining three pieces of garbage, and looked at only one. Clearly this is absurd, in like evidence based anything.[54] Here is novel evidence of whimsy-based medicine by definition (Upshur and Tracy 2004).[55]

It becomes more absurd when we look at the recommendation that came out of looking at this one piece of garbage: consider IV fluids standard care and acupressure for moderate to severe NVP. Why? Because NICE only saw one piece of very odious garbage.[56]

So one has seen (or not seen) the (R)CTs, or garbage, based upon which is the systematic reviews, guidelines, and guidline/reviews that is EBM. Garbage in the plural of course, but in the case of NICE the garbage was singular. Some items of garbage can be traced with or without difficulty and money, most items of garbage are invisible, they cannot actually be seen (as a discrete item of garbage, and not as an item in a garbage catalogue). In some cases the garbage was blenderdised. In other cases garbage was left as pieces of garbage, and with some dressing. It does not really matter because what me mostly see (hopefully without difficulty nor money) is either blenderdised garbage or reduced garbage plus dressing.

May one look at something else please? May one, for example, look at the experiences of health professionals in Western countries with acutherapy for NVP? No. Why not? Because. That's the way it is.

Since when, one may ask? Since when are experiences of Western physicians and more recently midwives, nurses, and maternity school professionals, since when is this body of knowledge labelled as experience

[54] For a truly excellent totally evidence based example of the absurd in EBM to do with guidelines, see (Messerli, Rimoldi, and Bangalore 2018): changing the definition of hypertension changed the status of millions in the US from hypertensive to normal overnight. And then changed the status of tens of millions in the US from normal to hypertensive another night.

[55] Upshur and Tracey (2004) could not have known of course that the *NICE guideline NG201* and *Green-top Guideline No.69* are by definition concretely whimsy-based.

[56] To place this in the medicine-in-literature tradition: The whole thing is Orwellian of course, but this particular absurdity of NICE outpatient self-administered *ad nauseaum*? I would say it is less Franz Kafka and more Italo Calvino.

of no importance as evidence for making guidelines, arguably for the whole world? The answer is: round about the same time Cochrane came into being (Greenhalgh, Howick, and Maskrey 2014).[57] And what Cochrane say, goes. No? No.

Obviously not. The National Institute for Health Research (UK) found the garbage Cochrane had blenderdised in addition to other garbage, did not blenderise, summarized or reduced those items of garbage, and put dressing (high bias, low confidence, *etc*.).

NICE totally ignored all garbage but one. Well, they found the (un)blenderdised garbage from Cochrane, the discretely dressed garbage from The National Institute for Health Research (UK), and much much more, and *then* ignored it.

The Royal College of Obstetricians & Gynaecologists (UK) had their own four items of garbage, visibility mixed.

So clearly what Cochrane say does not have to go. Cochrane is there for EBM but you can ignore it for the purpose of EBM.

Never mind for now *since when*, it is what it is. Why? Why is the body of knowledge labelled as experience in acutherapy management of NVP not admissible in EBM?

….

Oh dear. It gets complicated very quickly. All we want to know is why there is no role in EBM for the experiences of Western health professionals with acutherapy for NVP.

One easy answer is the nature of the knowledge itself:

"…The appeal to the authority of evidence that characterizes evidence-based practices does not increase objectivity but rather obscures the subjective elements that inescapably enter all forms of human inquiry…

…Against feminist misgivings about so-called objectivity, rationality, and value-neutrality, EBM proposes to introduce rational order into the deliberative processes of healthcare decision-making. The epistemic concerns of feminist scientists and philosophers are accompanied by a feminist commitment to improving the lives of women. Feminist critiques of science are driven by a deep concern that the abstractions made in the names of scientific objectivity, generalisability, and predictability harm women. These tendencies appear to resurface in the practice of EBM…"

(Goldenberg 2006) pages 2621 and 2627

[57] The references on distortion of evidence and vested interest are noteworthy. The discussion of other causes and effects of a 'crisis' in EBM appears reasonable. The remainder and majority on what we can do about all that is bombastic and tedious if endearing.

But that is too easy. 'Nature of knowledge' discussions are easily scoffed away, should anyone dare bring them forward, say in an EBM conference, with some variant of 'bitches be crazy' rule-of-thumb.[58]

Let us feign sanity. Let us ask EBM for evidence of experience of health professionals in the management of NVP on EBM's own terms, its own garbage, what is defined as evidence in EBM.

Well, we *did* agree to look at garbage which is absurd (us looking at garbage that is). So we might as well look only at some garbage, which is even more absurd (us deciding to look at some garbage but not other garbage, not us looking at garbage all). So let us just look at EBM garbage only. Why is there no garbage, discrete, reduced, blenderdised, why is there no garbage of any kind about experience in the EBM of NVP management?

We find that the nature of experience is not amenable to garbage-ification. EBM places experience and studies about experience very low in terms of legitimacy, hierarchy, and authority (Upshur and Tracy 2004).[59]

One gets the feeling we've been through this before. Way back in 1996 when Vickers huffed, 'What is it exactly that you want to see (and I'll show it you)!' and in 2002 when the Society of Obstetricians and Gynecologists of Canada (EBM or no?) said there is no such thing as a randomized acutherapy clinical trial, but that article is RETIRED and one is obliged not to use it for any purpose other than historical. Not to mention the tens of articles one may cite belabouring the placebo in acutherapy trials, the reviews of those, models, commentaries, and briefs alleging to have fatally debunked all the above.

Oh dear. I say again, it got complicated very quickly. All we wanted to know is why there is no role in EBM for the experiences of, for example, Western health professionals with acutherapy for NVP.

Let us not throw this question into GoogleScholar. Let us ask the producers of the key systematic reviews, and national and international guidelines themselves. That's narrowing it down. Let us ask these key producers of EBM: Why is there no role for the experiences of Western health professionals in EBM of acutherapy for NVP please?

Cochrane (Matthews and others) and the National Institute for Health Research (UK, O'Donnell and others) would reply that they use only

[58] The author here is referring to himself, though his wife may disagree.

[59] The study by Upshur and Tracy (2004) abstract: "…This paper examines four challenges that proponents of evidence-based medicine (EBM) must address to establish its claims to universality and legitimacy. It is argued that the failures to meet the evidence-of-effectiveness challenge, the authority challenge, the conflicting hierarchy challenge, and the definition-of-evidence challenge diminish arguments for the superiority of EBM. In the second part of the essay, recent developments in the theory of EBM are discussed with specific reference to what is termed the Oslerian turn, and a relationship between EBM and rationality is entertained…"

(R)CTs for analysis (blenderdised, or reduced and dressed, items of garbage, respectively). One does not come across double-blind randomized placebo-controlled clinical trials of experience in general, cross-over or no, let alone Western health professionals acutherapy *etc*. One would wonder about the validity of such a trial, should one ever come across such a thing. In any case, for the present, there are not any.

NICE may reply that, 'Pfff, everything was looked at, all the garbage out there anyone ever found, good luck seeing it'.

All that garbage was thrown out. 'We took the one piece of garbage'. Which one? 'The one that was not thrown out.' It exists as a discrete item of garbage without blenderification, nor reduction and dressing. It can be seen in its form as a discrete item of garbage without difficulty nor money so one may see it.

Wonderful, one has seen (Adlan, Chooi, and Mat Adenan 2017). One may allow for 'experience of health professionals' room in this item of garbage (an (R)CT, of course, that goes without saying) only in the most loose terms, imagination not recommended. It was said to be from Malaysia. That's a bit of a problem because it has to be relevant to the UK. So the other two studies NICE kinda looked at (for moderate to severe NVP only, mind you) and yeah there's an item of garbage or two from the UK…so…yeah. Experience.

Well and good. Experience is in the NICE EBM. The recommendation please, which of course includes evidence from the experiences of health professionals from around the world and of course from the UK. The recommendation is: IV fluids and acupressure for moderate to severe NVP. Is this recommendation in line with experience? Physiology even? Perhaps the answer is no.

The Royal College of Obstetricians and Gynaecologists (UK) would reply: *'Only* experience was considered!' Theirs, of course, and which leads one to the four items of garbage catalogued in Table 5. Which happens to be what we expect to see in that same truck of EBM garbage (acutherapy NVP), no experience except with the most loose imagination *etc*.

'A ha!' one may shout. So *in the experience of The Royal College of Obstetricians and Gynaecologists (UK)*, Cochrane is not to be trusted? The garbage from (Matthews et al. 2015) was not taken into consideration while developing *Green-top guideline No.69* in 2016.

Oh, that's embarrassing. But Matthews et al. (2010) was cited! It was? It is not in Table 5. So it was not cited in any context related to acutherapy for the management of NVP. In fact, Matthews et al. (2010) was first cited in the *Green-top guideline No.69* 2016 after the statement that "…HG is the

severe form of NVP, which affects about 0.3–3.6% of pregnant women…", along with three other references on page 5.[60]

Well, it does not matter because the Guideline was based on Fellows' experience, which does not have to include Cochrane, in fact Cochrane was brazenly ignored. Fair enough. But then this experience of the Royal College of Obstetricians and Gynaecologists (UK) is not EBM. And is petulant.

The answer from *Practice Bulletin No.189* is that in the experience of Erick, Cox, and Mogensen (2018), wristbands are recommended. The answer from *Pregnancy Care 2020 Edition* is probably rude, and anyways withheld until we actually do ask, in which case Matthews et al. (2010) was checked again in 2020 at least once, and nothing new was found, including Matthews et al. (2015). The answer from SOMANZ 2019 is that in the experience of Lowe et al. (2019a&b) acutherapy for management of NVP is not recommended and it is best not to look too closely at an article from Malaysia.

The answer from Society of Obstetricians and Gynecologists of Canada is that in the experience of Campbell et al. (2016), acutherapy is recommended but not worth putting in the treatment algorithm and ginger, psychotherapy, as well as diet and lifestyle are also not worth including in the treatment algorithm.

The *WHO 2016 Recommendations* are EBM, of course. So the garbage from Cochrane was taken as is? Not exactly. Developers at WHO did not like Cochrane's blenderization process, so took a little bit of all the hard work in Matthews et al. (2015), how Cochrane chooses the items of garbage that will go into the blender.[61] It is a little bit of the whole work, which includes searching for garbage, sorting it, finding out which items of garbage fit into your blender, and so on, and that is still a lot of work. So WHO took that little bit of a lot a lot of work and worked it again, one by one. Anyways, there is no knowledge of experience in the Cochrane garbage, so *WHO Recommendations* did not consider evidence of experience in acutherapy management of NVP.

Wait. What? WHO ignored experience? Of course not! Who could say such a thing. *WHO 2016 Recommendations* has whole *repeating* sections, sometimes *verbatim*, on Values, Acceptability, Preferences, and what not. And the reference is Downe and others, who said a lot of common sense things about being nice to mum and caring for her and making sure there's

[60] Interestingly one of those articles is 'Miller F. Nausea and vomiting in pregnancy: the problem of perception—is it really a disease? *Am J Obstet Gynecol* 2002;186 Suppl 2:S182–3'. One would hope that HG is not perceived to be a perceptual problem?

[61] The items of garbage, as we know by now, are mostly invisible, not seen in discrete form as opposed to abstracts or items in a garbage catalogue. What some may find invisible however could potentially be seen by WHO developers.

ethanol and cotton balls in the primary maternal clinic, anything we might really need to help these women anyway we can, heck some information would be *great*, like a guideline or something…wait…what? There *is* a guideline?

So once more, how does that guideline, how does *WHO Recommendations 2016* consider the experience of Western health practitioners with acutherapy for the management of NVP? The answer might look like 'it does not' because Cochrane sorted out experience from the garbage it selected, arguably by definition, so right at the very start, before the mega-search for (R)CTs was even launched. And there is no doubt that there is no health practitioner experience of acutherapy for the management of NVP in Cochrane EBM after experience was in any way defined. The fact that WHO reduced and dressed the items of garbage selected by Cochrane does not alter the fact that experience does not feature in said items of garbage.

Experience based evidence (not EBM) in *WHO Recommendations* comes from Downe and others. And somehow this is: acutherapy is alien, expensive, not very feasible, and not readily acceptable. One may not see how the work of Downe and others relates to the language in *WHO Recommendations*, let alone EBM.

Has the world gone mad? Is there no role for practitioner experience in EBM of acutherapy for the management of NVP?

'Of course NOT!' shouts the Expert Consensus from the College of French Gynecologists and Obstetricians (Deruelle et al. 2022). 'OUR national guideline states': "…If the PUQE score is < 6, even in the absence of proof of their benefit, ginger, pyridoxine (B6 vitamin), acupuncture or electrostimulation can be used, even in the absence of proof of benefit…". 'We obviously based OUR recommendations on our experience as well as that of professionals from maternity schools across France!'

Por le cul dieu. Why did you not speak out earlier?

One more question please. Why did you have to say 'in the absence of proof of benefit' – TWICE? Is your experience, the experience of professionals from across maternity schools, and numerous other colleagues from around the world, not *evidence (presence) of proof*? In other words, experience is absent by your own admission.

The role played by acutherapy for the management of NVP in key clinical publications and national and international guidelines is miserable because it is disconnected from experience.

This study ends here.

Afterword

The abstract of the 'confession' by (Ioannidis 2016) is dense with shocking allegations about EBM.

(Cairney and Oliver 2017) was serious about the gap in EBM policy making, but one gets lost somewhere. How can one be pragmatic about the absurd 'beliefs' of others? Well one can, perhaps, but it does not help EBM of NVP. See also (Haynes 2002).

(Ernst 2009) discusses absurdity in EBM. However the main arguments (how data moves from quackery to evidence) may work by replacing, for example, 'alternative therapies' with 'EBM'. Arguments that work the same way from left to right as right to left are interesting.

(Lundeberg et al. 2008) has a title that tried to be funny.

Shared decision making in EBM is celebrated in (Djulbegovic and Guyatt 2017).

An app to care for mum in (Ngo et al. 2022). More data needed.

(Wong et al. 2022) appeared to have analysed mostly Australian guidelines and a sense of frustration is mixed with what appears to be admirable restraint.

Nottinghamshire Area Prescribing Committee guideline click here.

The Royal Women's Hospital, Victoria Australia click here.

Royal College of Physicians of Ireland, Institute of Obstetrics and Gynecology guideline here.

News celebrating SOGC click here and here.

News celebrating NICE click here.

Paywalled guideline platform https://g-i-n.net/

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