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**Management of bone health in women with premature ovarian insufficiency:****Systematic appraisal of clinical practice guidelines and algorithm development**

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**Highlights**

- Clinical practice guidelines for the management of bone health in women with premature ovarian insufficiency demonstrate variable quality when they are evaluated using a standardised assessment tool (the AGREE II instrument).
- There is a paucity of high-quality evidence to guide management.
- Clinical practice guidelines recommend institution of hormone replacement therapy (unless contraindicated) at least until the age of usual menopause in women with premature ovarian insufficiency.

**Abstract**

*Background:* Osteoporosis is a key concern of women with premature ovarian insufficiency (POI) but there are gaps in clinicians' knowledge of bone health.

*Objectives:* 1) To systematically evaluate the quality of clinical practice guidelines (CPGs) related to POI and bone health; 2) to formulate a management algorithm.

*Methods:* Systematic search for English-language clinical practice guidelines (CPGs) from August 2012 to August 2017 (PROSPERO registration number CRD42017075143). Four reviewers independently evaluated the methodological quality of included CPGs using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (comprising 23 items across 6 domains) using the My AGREE PLUS platform. Inter-rater reliability was assessed using the intraclass correlation coefficient (ICC). Individual domain and total percentage scores were calculated for each CPG. Data from high-scoring CPGs were extracted and summarised to develop the algorithm, with subsequent refinement via expert and end-user clinician feedback.

*Results:* The systematic search yielded 16 CPGs for appraisal. ICC values were 0.71 (good) to 0.95 (very good). The quality of the CPGs was appraised as "high" in 4 cases, "average" in 8 and "low" in 4. High-quality CPGs had mean total scores of 82-96%. Recommendations from high-quality CPGs were summarised into 6 categories: screening; risk factors; initial assessment; diagnosis; subsequent assessment; and management. Only "management" had recommendations (moderate-quality to low-quality evidence) from all four high-quality CPGs. Limitations are reflected in the algorithm.

*Conclusions:* Most CPGs regarding bone health and POI are of average to poor quality. High-quality CPGs have evidence limitations and recommendation gaps indicating the need for further research.

## **Keywords**

Premature ovarian insufficiency. Bone. Clinical practice guidelines. Algorithm.

Osteoporosis.

## **1. Introduction**

Premature Ovarian Insufficiency (POI) can be spontaneous or iatrogenic and is defined as loss of ovarian function with development of hypergonadotropic hypogonadism in women under the age of 40 years [1]. Spontaneous POI affects approximately 1% of women and is associated with genetic defects, autoimmune disorders, environmental factors and infections, but is most commonly idiopathic [2-3]. Iatrogenic POI can occur secondary to surgical intervention (E.g. bilateral oophorectomy), chemotherapy and/or radiotherapy [2,4].

The effects of oestrogen deficiency include menopausal symptoms such as: vasomotor symptoms, insomnia, mood lability, and vulvo-vaginal atrophy. Longer-term consequences of POI include an increased risk of cardiovascular disease and mortality, accelerated cognitive impairment, infertility and osteoporosis [2,4-6]. Women with POI have a significantly lower bone mineral density (BMD) [2,4,7-13] and a 1.5-fold greater risk of fracture compared to women who experience menopause at the typical age [14-16].

The estimated prevalence of osteoporosis in women with POI is approximately 8-14% [2,13]. Sex-steroids contribute to skeletal homeostasis during growth and adulthood. Bone loss starts after achieving peak bone mass regardless of changes

in sex steroid concentrations but the sharp decline of oestrogen levels at menopause accelerates bone loss and leads to deterioration in bone microarchitecture [7-8].

Clinical practice guidelines (CPGs) are being increasingly used by clinicians to assist patient management [17-20]. They encompass statements to aid clinicians' decisions regarding appropriate care for specific clinical circumstances [17-18]. The benefits of using CPGs can include improved consistency of care and quality of clinical decisions by offering recommendations for clinicians who are uncertain how to proceed, updating outdated practices and providing reassurance about appropriateness of treatment based on authoritative recommendations [19]. Adherence to CPGs has been shown to improve the process of care as well as patient outcomes [20]. However, implementation of poor-quality guidelines may be detrimental to the patient and the health care system [17-18]. Many existing CPGs lack high-quality evidence and rigorous methodology, compromising their integrity [17-18,21].

Women with POI are cared for by a variety of clinicians whom are not necessarily specialists in bone health including primary care providers, gynecologists and endocrinologists. High-quality CPGs could be useful to simplify decision-making and provide more consistent care for these women. To date, there are numerous publications related to managing bone health in women with POI derived from varying sources, which are of unknown quality [1-2,21-36]. This may contribute to the observed variations in clinical practice and clinician knowledge gaps regarding management of POI, including bone health [37].

The aim of this study was to review the methodological quality of contemporary CPGs regarding bone health in women with POI and, using these findings, formulate a management algorithm to guide treating clinicians.

## 2. Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered with The International Prospective Register Of Systematic Reviews (PROSPERO) (Registration number CRD42017075143). A systematic review was conducted of contemporary CPGs in which management of bone health in POI was addressed.

### *2.1 Search methods for identification of guidelines*

A comprehensive search of electronic databases, guideline repositories, the websites of relevant professional societies and the grey literature was conducted (Supplement 1). The bibliographies of retrieved guidelines were manually reviewed for identification of additional potentially relevant guidelines.

The search was conducted in August and September 2017. A sensitive search strategy was used, combining relevant subject indexing and free text terms for “guideline”, “premature ovarian insufficiency” and “bone”. The search was limited to English language, human subjects and publication date of August 2012 to August 2017. The detailed search strategy is provided in Supplement 2.

### *2.2 Eligibility criteria and selection process*

Two independent reviewers (SDC and AV) screened the titles and abstracts of the retrieved records to identify their eligibility for inclusion. The latest version of national and international CPGs, recommendations, position statements, consensus statements and development conferences, which provided guidance on osteoporosis prevention and management in women with POI or early menopause were included. We excluded systematic reviews, randomised controlled trials (RCTs), controlled (non-randomised) clinical trials, case-control, prospective and retrospective cohort and cross-sectional studies, case reports, pilot and feasibility studies, narrative

reviews, scientific reports, commentaries, conference abstracts and posters. Selected guidelines were reviewed to verify eligibility (Figure 1). Guidelines were excluded if they included women with menopause diagnosed after age 45 years. Any disagreement was resolved by discussion to reach consensus.

### *2.3 Quality assessment*

The quality of the guidelines was evaluated using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument [38]. This instrument is designed to appraise the quality of health-related CPGs by evaluating the methodological quality. It consists of 23 items organized in six domains: 1) Scope and Purpose (items 1-3), 2) Stakeholder Involvement (items 4-6), 3) Rigor of Development (items 7-14), 4) Clarity of Presentation (items 15-17), 5) Applicability (items 18-21) and 6) Editorial Independence (items 22-23), with each item rated on a seven-point Likert scale [38]. A score of 1 was given for strongly disagree, 2-6 indicating the full criteria has not been met and 7 meant strongly agree indicating that the quality of reporting is exceptional, and all criteria and consideration articulated in the user's manual were met. These six domains are followed by two additional items forming an Overall Assessment, which includes "the rating of the overall quality of the guidelines and whether the guidelines would be recommended for use in practice" [38].

Four independent reviewers (SDC, AV, GS and FM) scored each of the CPGs according to the AGREE II instrument via the My Agree Plus online platform, which they had been trained to use through the user manual [38]. Total scores for each domain were calculated by summing up the scores of the individual items within the domain and scaling them as a percentage of the maximum possible score for that domain, expressed as mean  $\pm$  Standard Deviation (SD) [38]. Similar to previous studies, the quality of CPGs was defined as follows: high-quality when 5 or more

domains scored >60%, average-quality when 3 or 4 domains scored >60%, low-quality when  $\leq 2$  domains scores >60% [30,39].

#### *2.4 Data analysis*

Descriptive statistics was performed using Microsoft Excel 2013 (Redmond, Washington, USA). The inter-rater reliability analysis was performed to assess the degree of agreement between reviewers using the intraclass correlation coefficient (ICC) with a 95% confidence interval (CI). The scores were defined as: poor 0.0-0.2, fair 0.21-0.4, moderate 0.41-0.6, good 0.61-0.8 and very good 0.81-1.00. Where the  $ICC < 0.70$ , domain scores were discussed by the reviewers and a consensus made. The reliability analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0.

#### *2.5 Development of the algorithm*

Recommendations specifically related to women with POI from the highest scoring CPGs were summarized into six categories related to bone health: 1) Screening; 2) Risk Factors for Developing Low BMD; 3) Initial Assessment of Bone Health; 4) Diagnosis of Low BMD; 5) Subsequent Assessment of Bone Health; and 6) Management. These recommendations were then used to develop a draft management algorithm. The draft algorithm was reviewed by expert endocrinologists (AV and FM) and then refined following stakeholder feedback from gynaecologists, general practitioners and endocrinologists (n=9) to achieve the final version (Figure 2)

### **3. Results**

Our search identified 145 records, 16 of which met our inclusion criteria (Figure 1) and characteristics of included CPGs are presented in Table 1.



### 3.1 Methodological quality of CPGs

AGREE II scoring for each domain and final assessment of overall quality of the included CPGs is summarised in Table 2. The inter-rater reliability using the intraclass correlation coefficient values ranged from 0.71 (good) to 0.95 (very good). In eight instances the ICC was  $<0.70$ , thus domain scores were re-discussed by reviewers to achieve greater concordance and ICC scores re-calculated.

High-quality CPGs were those developed by the National Institute for Health and Care Excellence (NICE) [22], European Society of Human Reproduction and Embryology (ESHRE) [1], Scottish Intercollegiate Guidelines Network (SIGN) [23] and The Endocrine Society [24], with mean total scores of 96%, 93%, 91% and 82% respectively. The NICE guideline ranked the highest with scores  $\geq 88\%$  in all six domains. Eight average quality CPGs were identified (score range 56-74%) and four low quality (score range 40-58%). According to overall quality, four CPGs were considered “recommended”, eight “recommended with modification” and four “not recommended”.

Highest mean scores were obtained for Domain 1 (Scope and Purpose) and Domain 4 (Clarity of Presentation) at 85% (range 68-100%) and 87% (range 58-100%) respectively. NICE [22], ESHRE [1] and Endocrine Society [24] CPGs achieved maximum scores for Domain 1 and ESHRE [1] and The Endocrine Society [24] for Domain 4. The lowest mean score (44%; range 22-96%) was observed for Domain 5 (Applicability). A mean score of 58% was observed for Domain 2 (Stakeholder Involvement); the SIGN [23] (97%) and ACOG [25] (25%) being the highest and lowest scoring CPGs respectively. Domain 3 (Rigor of Development) was similar to Domain 2 with a mean score of 57% (range 30-99%) and the NICE CPG [22] was the highest scoring guideline. A mean score of 70% (range 15-98%) was observed

for Domain 6 (Editorial Independence), with ESHRE [1] guidelines scoring the highest.

### *3.2 Guideline content and algorithm development*

Recommendations from the highest four scoring guidelines (NICE, ESHRE, SIGN, The Endocrine Society [1,22-24]) were summarised into six categories related to bone health: 1) Screening; 2) Risk Factors for Developing Low BMD; 3) Initial Assessment of Bone Health; 4) Diagnosis of Low BMD; 5) Subsequent Assessment of Bone Health; and 6) Management (Table 3).

Content of these four highest scoring CPGs varied regarding the scope of recommendations pertaining to bone health. The most comprehensive guideline was ESHRE [1] with recommendations in all six categories. Two of the CPGs focused only on the management of bone health and had no recommendations for the other categories [22,24]. The quality of evidence in the guideline recommendations ranged from low to moderate quality (Table 3). The highest quality of evidence was of moderate quality from the ESHRE [1] guideline pertaining to “Initial Assessment of Bone Health” and “Management”.

Only the ESHRE [1] CPG had recommendations for “Screening” suggesting that assessment of BMD should be considered in all women at POI diagnosis.

Two CPGs had comments regarding “Risk Factors” in women with POI for developing low BMD. ESHRE [1] had discussion-based comments with no firm recommendation or grading of evidence, whereas the SIGN [23] CPG had recommendations from case reports/series (level 3 evidence) specific only to childhood cancer survivors (Table 3).

Regarding “Initial Assessment of Bone Health”, the ESHRE [1] CPG suggested assessment of BMD with Dual-Energy X-ray Absorptiometry (DXA) at diagnosis in all

women with POI based on moderate quality evidence, whereas the SIGN [23] guideline specific to survivors of childhood cancer suggested BMD assessment 2 years following cessation of cancer treatment. The other guidelines had no recommendations.

There was a paucity of evidence pertaining to the diagnosis of low BMD with no clear guidance from any CPG regarding the best way to define this.

“Subsequent Assessment of Bone Health” were only included in the ESHRE [3] and SIGN [23] CPGs. Based on low quality evidence, these CPGs suggested repeat assessment of BMD in non-childhood cancer survivors within 5 years following treatment initiation.

The “Management” category was the most comprehensive with similar recommendations from all four CPGs, which included commencing oestrogen replacement, if no contraindications, at diagnosis until at least the time of usual menopause.

Feedback for the algorithm was completed by 9 stakeholders (2 gynaecologists, 4 general practitioners, 3 endocrinologists) with minor refinements incorporated to produce the final version. Evaluations for the content regarding all sections of the algorithm ranged from ‘very good’ to ‘excellent’. All clinicians reported that the algorithm was helpful and they would use it if freely available.

#### **4. Discussion**

Our systematic search and AGREE II appraisal of CPGs related to POI and bone health indicates variability in quality domains between guidelines. Of the 16 CPGs evaluated, only four were assessed as high-quality and recommended by reviewers. Analysis of CPG content revealed variability and a paucity of high-quality evidence to

guide management. Despite these limitations, a management algorithm to assist clinicians in the management of bone health in POI was developed and refined.

The finding of “Clarity of Presentation” and “Scope and Purpose” as the highest scoring domains is comparable to other studies using the AGREE II instrument to evaluate guidelines related to a variety of conditions [39-41]. A recent systematic review assessing the factors associated with the quality of 421 CPGs related to the management of common diseases in primary care using the AGREE II instrument, similarly found these two domains to have the highest mean scores [42]. “Applicability” was the lowest scoring domain in our and other studies [40-42]. “Applicability” relates to the ability of the CPG to describe barriers to application and to give advice as to how the recommendations can be put into practice and monitored [38]. The low score in this domain may reflect greater resource investment into development than application and an under appreciation of the importance of CPG implementation and outcome monitoring [42-43]. Effective implementation programs of CPGs with primary treating clinicians have been shown to improve treatment targets [44], whilst CPGs with low applicability can limit compliance with the proposed recommendations [42]. The only guideline, which suggested barriers to implementation was the NICE guideline [22]. A high score in the domain “Rigor of development” indicates sound evidence-based guideline development and minimum bias. A systematic review on 118 publications reporting guideline appraisals with AGREE II found “Rigor of development” to have the strongest influence on overall guideline quality [46]. This is demonstrated in our study with the ranking of the highest to lower quality CPGs reflecting their scores for this domain.

“Editorial independence” was the third highest scoring domain in our study contrasting with other studies where it was the lowest scoring [39,41]. This was

reassuring given that conflicts of interest among authors of guidelines may affect the quality of recommendations [39,41].

Knowledge gaps related to bone health management in POI were evident in the summary of CPG recommendations. Moderate quality evidence suggests that assessment of BMD with DXA scan should be considered for all women diagnosed with POI. However, only 35.9% of women with POI attending outpatient clinics at a UK teaching hospital had their BMD measured after diagnosis [47]. This may reflect poor implementation, consistent with the low “Applicability” scores in most CPGs.

Identification of risk factors for developing low BMD in women with POI are derived from observational studies with methodological limitations and the CPGs reflect this uncertainty [23]. Risk factors for low BMD in women with POI vary depending on aetiology. Identified risk factors for low BMD ( $Z$  score  $< -2$ ) in women with spontaneous normal karyotype POI included: age  $< 20$  years at onset of irregular menses,  $> 1$  year delay in diagnosis, low serum vitamin D concentrations, low dietary calcium, non-compliance with oestrogen replacement and lack of exercise [9]. In contrast, women with Turner Syndrome have additional contributors to bone loss, skeletal fragility and falls risk; including genetic, hearing loss, coeliac disease and visuo-spatial abnormalities [48]. Women with breast cancer and iatrogenic POI have the additional risk factor of aromatase inhibitor therapy [49].

Diagnosis of low BMD and osteoporosis in young adults is challenging [8]. None of the CPGs provided specific recommendations on how to diagnose low BMD in POI. The use of DXA-derived BMD T-score to diagnose osteoporosis can generally not be used until peak bone mass has been achieved [8]. Additionally, areal BMD can be underestimated in individuals with short stature such as women with Turner Syndrome [1,9]. The 2019 International Society for Clinical Densitometry position

statement recommend that Z-scores  $<-2$  be used to define low bone mass in women before menopause; however, it does not specifically refer to women with premature menopause/POI [50]. An International Osteoporosis Foundation review of osteoporosis in young adults proposes that Z score  $<-2$  be used to define low bone mass in young adult (pre-menopausal women); however, maintaining the use of T-score  $<-2.5$  to diagnose osteoporosis in young adults suffering from chronic disorders known to affect bone metabolism [8]. Fracture risk assessment tools, such as FRAX, are not validated for women under age 40 years.

Management of bone health was addressed in the four highest scoring guidelines; however, supporting evidence was predominately moderate to low-quality. Non-pharmacological management recommendations were only reported in the ESHRE CPG and were extrapolated from evidence related to lifestyle modification and fracture risk in postmenopausal women [1]. The SIGN CPG identified an observational study of childhood cancer survivors which indicated that BMD is improved by exercise [23]. Hormone replacement therapy (HRT) was recommended by all four highest scoring guidelines. Interestingly the highest scoring guideline, NICE, had recommendations in no other category apart from management of bone health in women with POI, outlining the limitations of the AGREE II instrument and the inability of this tool to evaluate content [22]. A recent meta-analysis, including both observational and randomised controlled studies of women with different causes of POI, concluded that HRT increased lumbar spine BMD with inconclusive evidence regarding hip BMD or fractures and variable response depending on the cause of POI [51]. A meta-analysis assessing HRT in women with Turner syndrome indicated increased lumbar spine BMD with oestradiol containing HRT but not ethinyl-oestradiol or conjugated oestrogens [52]. The general consensus from the

CPGs was that women diagnosed with POI should commence oestrogen replacement at diagnosis, with oestradiol preparations potentially having more favourable effects on BMD, and should be continued at least until the age of natural menopause [1,22-24].

The ESHRE CPG recommends that other pharmacological interventions, including bisphosphonates should be considered with advice from an osteoporosis specialist and particular caution applies to women desiring pregnancy [1]. A small study (n=60) of women with POI secondary to chemotherapy for allogeneic stem cell transplant indicated that bisphosphonate therapy for 12 months increased lumbar spine BMD whereas HRT did not [53].

Only two guidelines provided recommendations for subsequent assessment of bone health based on clinical experience and expert opinion only, reiterating the lack of evidence in this field [1,23].

A management algorithm was developed based on the recommendations of the four highest scoring guidelines, with refinement by experts in the field as well as potential end-users. Algorithm recommendations related to screening and risk assessment, initial and subsequent assessment of bone health and diagnosis of low BMD were largely formulated from two out of the four top scoring guidelines [1,22], mainly from the ESHRE CPG, as the remaining CPGs did not offer recommendations in these areas. This proposed algorithm is limited by the gaps and quality of evidence of the four guidelines on which it is based. Women with POI report osteoporosis as one of the most feared consequences of POI [54-55]. This highlights the urgent need for research directed at overcoming the identified knowledge gaps to facilitate optimal bone health.

Study strengths included use of (i) an extensive search strategy, (ii) a validated tool (AGREE II) to grade CPG methodological quality, (iii) multiple trained appraisers scored the CPGs, (iv) high inter-observer agreement and (v) clinician input to refine the algorithm. Our study was limited in that (i) only English language CPGs were included, and (ii) the AGREE II instrument, robust to assess CPG methodological quality, does not evaluate content or the degree of consistency between CPG recommendations and the reported evidence.

## **5. Conclusion**

Most CPGs regarding bone health in women with POI are of average to poor-quality with significant limitations in most AGREE II domains. The AGREE II instrument could assist CPG development to optimize quality and also when deciding which CPGs to implement in clinical practice. The limited evidence underpinning recommendations indicates the need for further research. From the available evidence and with stakeholder engagement, we have devised a management algorithm to aid clinicians in the management of bone health in women with POI.

## **Contributors**

Velislava Kiriakova participated in the data analysis and interpretation, and the drafting and revision of the manuscript.

Shamil D Cooray participated in the study design, data acquisition and analysis, and the drafting and revision of the manuscript.

Ladan Yeganeh participated in the data analysis, and the drafting and revision of the manuscript.

Gowri Somarajah participated in data acquisition and revision of the manuscript.

Frances Milat participated in all aspects of preparation of the manuscript.

Amanda J Vincent participated in all aspects of preparation of the manuscript.



All authors saw and approved the final version of the manuscript.

### **Conflict of interest**

Amanda J Vincent serves on the editorial board of the journal *Climacteric*, which published one of the clinical practice guidelines in the study.

All other authors declare that they have no conflict of interest.

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### **Ethical approval**

This study did not involve experimentation with human subjects and therefore informed consent and ethical approval was not required.

### **Provenance and peer review**

This article has undergone peer review.

### **Research data (data sharing and collaboration)**

There are no linked research data sets for this paper. Data will be made available on request.

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### **Ethical statement**

This study did not involve experimentation with human subjects and therefore informed consent and ethical approval was not required.

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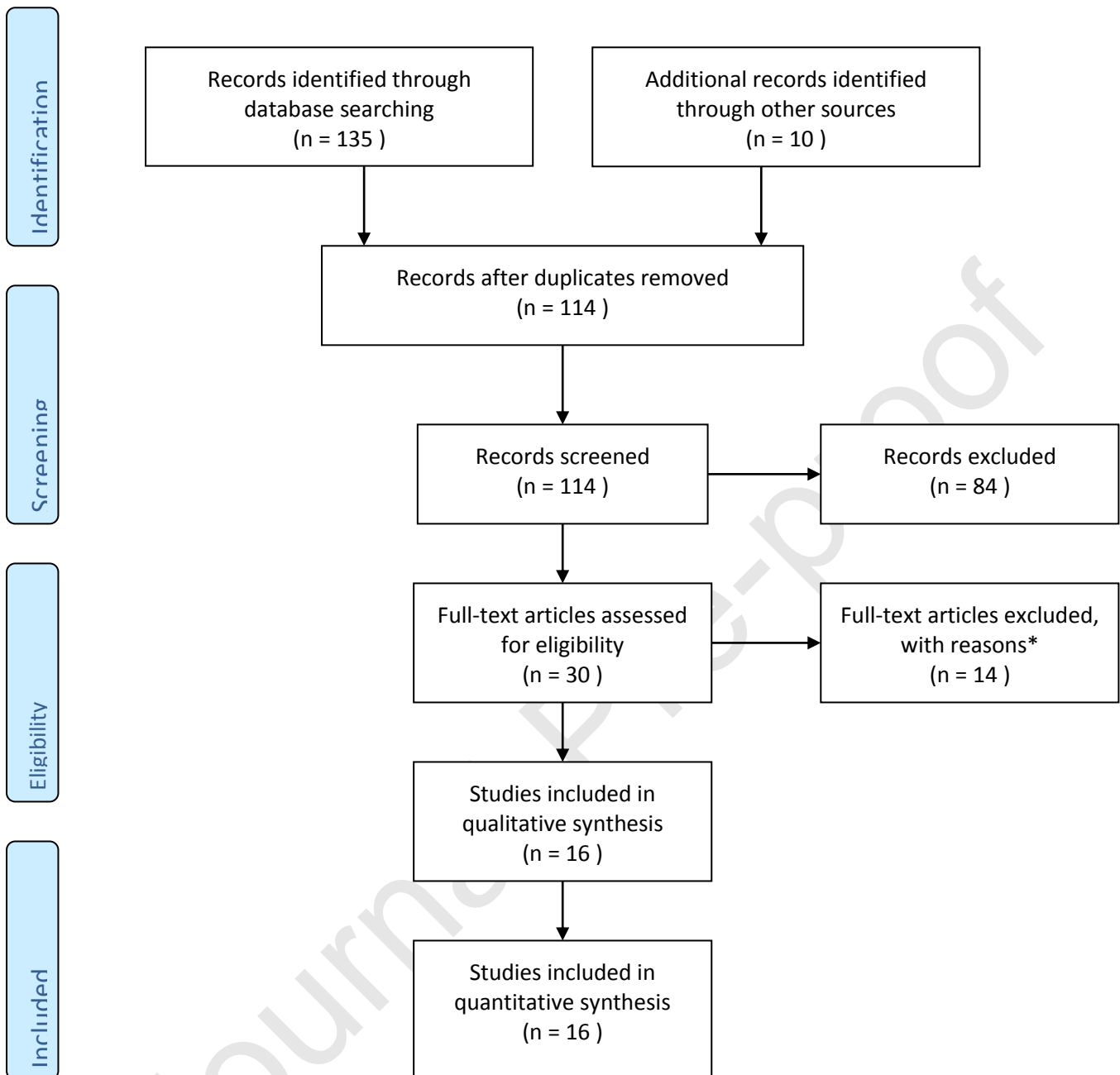
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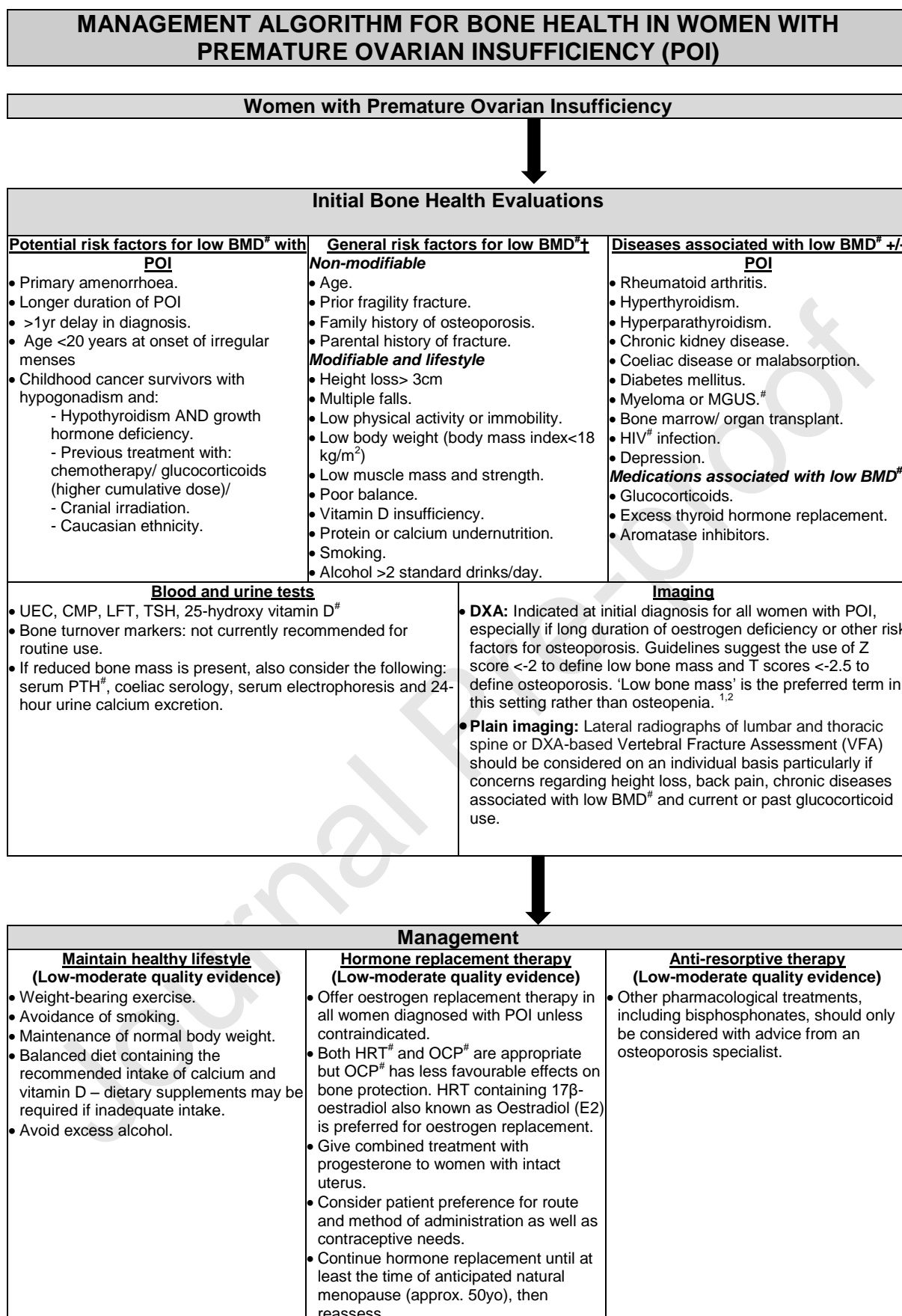
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**Figure 1:** PRISMA flow diagram of included studies

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

\*Reasons for exclusion: wrong patient population (n =6), not a CPG (n = 5), superseded by updated guidelines (n = 2), summary of full CPG (n = 1)

Figure 2: Management algorithm





<b>Further Assessment</b>	
<p style="text-align: center;"><b><u>Subsequent assessment of bone health</u></b></p> <ul style="list-style-type: none"> <li>• If BMD<sup>#</sup> is normal and adequate systemic oestrogen replacement is commenced, the value of repeated DXA<sup>#</sup> scan is low.</li> <li>• If a diagnosis of low bone mass is made and oestrogen replacement or other therapy initiated, repeat DXA<sup>#</sup> in 2-5 years.</li> </ul>	<p style="text-align: center;"><b><u>Specialist referral</u></b></p> <ul style="list-style-type: none"> <li>• A decrease in BMD<sup>#</sup> on subsequent scans (bone loss &gt;5% and/or &gt;0.05g/cm<sup>2</sup>) should prompt review of oestrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.</li> <li>• Development of a fragility fracture should prompt referral to an osteoporosis specialist.</li> </ul>

† FRAX risk calculator is not validated for use in women < 40 years

<sup>#</sup> BMD – Bone mineral density, MGUS – Monoclonal gammopathy of undetermined significance, HIV – Human immunodeficiency virus, CMP - Calcium, magnesium, phosphate, UEC - Urea, electrolytes, creatinine, LFT - Liver Function tests, TSH - Thyroid stimulating hormone, PTH – Parathyroid hormone, HRT – Hormone replacement therapy, OCP – oral contraceptive pill, FRAX – Fracture risk assessment tool

1. ESHRE Guideline Group on POI, et al. "ESHRE Guideline: management of women with premature ovarian insufficiency." *Human Reproduction* 31.5 (2016): 926-937.

2. Ferrari, S., et al. "Osteoporosis in young adults: pathophysiology, diagnosis, and management." *Osteoporosis International* 23.12 (2012): 2735-2748

**Table 1:** Characteristics of guidelines included in analysis

<b>Title of Guideline</b>	<b>Year of publication</b>	<b>Country of origin</b>	<b>Organisation</b>
Menopause [25]	2015	UK	National Institute for Health and Care Excellence (NICE)
Management of women with premature ovarian insufficiency [3]	2015	European	European Society of Human Reproduction and Embryology (ESHRE)
Long term follow up of survivors of childhood cancer – a national clinical guideline [26]	2013	Scotland	Scottish Intercollegiate Guidelines Network (SIGN)
Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline [27]	2015	Multinational	The Endocrine Society
Managing Menopause [37]	2014	Canada	The Society of Obstetricians and Gynaecologists of Canada (SOGC)
The 2017 hormone therapy position statement of The North American Menopause Society [35]	2017	USA	The North American Menopause Society (NAMS)
2016 IMS Recommendations on women's midlife health and menopause hormone therapy [31]	2016	UK	International Menopause Society (IMS)
The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer [33]	2012	European	The European Society of Breast Cancer Specialists
Spanish consensus on premature menopause [34]	2015	Spain	Spanish Menopause Society, Spanish Fertility Society, Spanish Contraception Society, Spanish Medical-Oncologic Society
First international consensus guidelines for breast cancer in young women (BCY1) [36]	2014	European	European School of Oncology (ESO), European Society of Breast Specialists (EUSOMA).
The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency [29]	2017	UK	British Menopause Society (BMS)
The British Menopause Society & Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women [32]	2016	UK	British Menopause Society (BMS)
Cancer-associated bone disease [38]	2013	Multinational	International Osteoporosis Foundation (IOF) and National Osteoporosis Foundation 2013
EMAS position statement: The ten point guide to the integral management of menopausal health [30]	2015	European	European Menopause and Andropause Society (EMAS)
Guidelines for menopausal hormone therapy: Recommendations of the Polish Menopause and Andropause Society – state of	2014	Poland	Polish Menopause and Andropause Society

knowledge as of December 2013 [39]			
Committee Opinion No. 698: Hormone Therapy in Primary Ovarian Insufficiency (ACOG) [28]	2017	USA	The American College of Obstetricians and Gynecologists (ACOG)

**Table 2:** Domain scores and overall assessment of Premature Ovarian Insufficiency and osteoporosis guidelines using AGREE II instrument

Guideline title/Organisation	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigour of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence	Total score Mean (SD) (%)	Overall quality	Whether to recommend
Menopause: diagnosis and management (NICE) <sup>25</sup>	100%	96%	99%	99%	96%	88%	96 (5)	High	Recommended
Management of women with premature ovarian insufficiency (ESHRE) <sup>3</sup>	100%	96%	93%	100%	74%	98%	93 (10)	High	Recommended
Long term follow up of survivors of childhood cancer (SIGN) <sup>26</sup>	99%	97%	92%	97%	88%	73%	91 (10)	High	Recommended
Treatment of Symptoms of the Menopause (The Endocrine Society) <sup>27</sup>	100%	61%	82%	100%	51%	96%	82 (21)	High	Recommended
Managing Menopause (SOGC) <sup>37</sup>	99%	65%	78%	96%	49%	56%	74 (21)	Average	Recommended with modification
The 2017 hormone therapy position statement of NAMS <sup>35</sup>	88%	49%	68%	97%	42%	94%	73 (24)	Average	Recommended with modification
2016 Recommendations on women's midlife health and menopause hormone therapy <sup>31</sup>	78%	67%	56%	88%	42%	83%	69 (18)	Average	Recommended with modification
The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer <sup>33</sup>	79%	60%	51%	88%	35%	65%	63 (19)	Average	Recommended with modification
Spanish consensus on premature menopause <sup>34</sup>	78%	43%	40%	75%	23%	90%	58 (26)	Average	Recommended with modification
First international consensus guidelines for breast cancer in young women (BCY1) (ESO, EUSOMA) <sup>36</sup>	79%	46%	49%	81%	25%	67%	58 (22)	Average	Recommended with modification
The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency <sup>29</sup>	85%	31%	30%	83%	28%	88%	57 (30)	Average	Recommended with modification
The British Menopause Society &	68%	36%	35%	82%	34%	81%	56 (23)	Average	Recommended with



Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women <sup>32</sup>									modification
Cancer-associated bone disease (IOF) <sup>38</sup>	81%	44%	44%	83%	35%	58%	58(20)	Low	Not recommended
The ten point guide to the integral management of menopausal health (EMAS) <sup>30</sup>	79%	57%	30%	58%	28%	88%	57 (25)	Low	Not recommended
Guidelines for menopausal hormone therapy: Recommendations of the Polish Menopause and Andropause Society <sup>39</sup>	82%	49%	36%	76%	35%	13%	48(27)	Low	Not recommended
Committee Opinion No. 698: Hormone Therapy in Primary Ovarian Insufficiency (ACOG) <sup>28</sup>	68%	25%	31%	82%	22%	15%	40(28)	Low	Not recommended
<b>Mean (SD) (%)</b>	85 (11)	58 (22)	57 (25)	87 (11)	44 (23)	70 (26)			

**Table 3:** Summary of recommendations from highest scoring CPGs for assessment and management of bone health in women with POI

Title of guideline	Screening	Risk factors (RF) in women with POI for developing low BMD	Initial assessment of bone health	Diagnosis of low bone mineral density	Subsequent assessment of bone health	Management
<b>Menopause: diagnosis and management (NICE)<sup>25</sup></b>	No recommendation.	No details.	No recommendation.	No recommendation.	No recommendation.	1. Offer sex steroid replacement - HRT or OCP (combined oral contraceptives) unless contraindicated. - Both HRT and OCP offer bone protection. - If contraindications to HRT/OCP give women advise on bone, CV health and symptom management. (low-very low quality of evidence) 2. Consider referring women with POI to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition. (Low-very low quality of evidence)
<b>Management of women with premature ovarian insufficiency (ESHRE)<sup>3</sup></b>	1. Measurement of BMD at initial diagnosis of POI should be considered for all women. (C) - Initial assessment of bone health may include DXA scan to provide a baseline measurement.	<i>Included as a comment but no recommendation/grading:</i> Factors associated with low BMD: - Primary amenorrhoea. - Longer duration of POI - >1yr delay in diagnosis. - Age <20 years at onset of irregular menses. - Low body mass index (BMI). - Low serum vitamin D. - Low dietary calcium intake. - Lack of exercise. - Non-compliance with oestrogen replacement	1. Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially where there are additional risk factors. (C) - If the duration of POI is short and oestrogen therapy has been initiated it is unclear whether DXA should be done	<i>Included as a comment but no recommendation/grading:</i> 1. BMD >2.5 standard deviations below peak BMD for the appropriate reference group (i.e. young women from the same population).	1. If BMD is normal on initial DXA and adequate systemic oestrogen replacement is commenced the value of repeated DXA scan is low. (GPP) 2. If a diagnosis of low BMD is made and oestrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years. (GPP) - A decrease in BMD	1. Women should maintain a healthy lifestyle to optimise bone health involving weight-bearing exercise, avoidance of smoking and maintenance of normal body weight. (GPP) 2. A balanced diet containing the recommended intake of calcium and vitamin D is recommended. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake and may be of value in women with low BMD. (C) 3. Oestrogen replacement is recommended to maintain bone health and prevent osteoporosis and it is plausible that it will reduce the risk of fracture. (C) - The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable. (C) - 17 $\beta$ -oestradiol is preferred to ethinylestradiol or conjugated equine oestrogens for oestrogen replacement. (C) - Progestogen should be given in combination with oestrogen therapy to

			in all women. - If long duration oestrogen deficiency or other RF (history of low impact fractures) should have baseline DXA assessment.		should prompt review of oestrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate. (GPP)	protect the endometrium in women with an intact uterus. (B) - Whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment. (GPP) 4. Consider patient preference for route and method of administration of each component of HRT when prescribing, as well as contraceptive needs. (GPP) 5. Once established on therapy, women with POI on HRT should have a clinical review annually, paying particular attention to compliance. (GPP) 6. HRT should be continued until at least the age of natural menopause to minimise control future cardiovascular and cognitive risk. (C) 7. Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. (C)
<b>Long term follow up of survivors of childhood cancer (SIGN)<sup>26</sup></b>	No recommendation.	RF associated with low BMD in childhood cancer survivors with hypogonadism: (3) 1. Hypogonadism AND hypothyroidism AND growth hormone deficiency. 2. Bone marrow transplant. 3. Treatment with; chemotherapy or glucocorticoids (higher cumulative dose increases risk). 4. Cranial irradiation. 5. Genetic polymorphisms in certain receptor of corticotrophin-releasing hormone receptor 1 gene and vitamin D receptor gene. 6. Caucasian ethnicity. 8. Physical inactivity. 9. Poor nutrition intake and Vitamin D.	1. Childhood cancer survivors whose treatment puts them at risk of endocrine dysfunction should have a baseline BMD at around 2 years after completion of treatment. (D)	1. When interpreting results of BMD should consider whether a patient's final height is compromised and the possibility of pubertal delay. (✓)	1. For survivors of childhood cancer repeating bone density in patients with results in normal range is not needed unless there is a clinical change in situation. (✓)	For survivors of childhood cancer: 1. No evidence on lifestyle modification improving BMD in these patients. (3) 2. Are at risk of hypogonadism and, in the absence of contraindications, sex steroid replacement therapy should be optimised. (3) 3. Endocrine evaluation is recommended for childhood cancer survivors who have a significant reduction in bone mineral density and/or recurrent fractures. (✓)
<b>Treatment of Symptoms of the Menopause (The Endocrine Society)<sup>27</sup></b>	No recommendation	No details	No recommendation	No recommendation	No recommendation	1. For young women with POI, without contraindications, suggest taking menopausal hormone therapy (MHT) until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2/XXOO) 2. For younger women with surgical menopause or those with POI who are accustomed to higher baseline endogenous oestradiol levels, clinicians often prescribe higher starting doses of oestrogen therapy and then slowly lower the dose as tolerated. - When women with premature menopause approach the age of natural menopause, reasonable to reassess and taper dose of MHT.

1

## 1 Grades of recommendation and levels of evidence

	Grades of recommendation		Level of evidence	
Endocrine Society Clinical Practice	1	Strong recommendation	XXXX	High-quality evidence
	2	Weak recommendation	XXXO	Moderate-quality evidence
			XXOO	Low-quality evidence

Guidelines		XOOO	Very low quality evidence
<b>Long term follow up of survivors of childhood cancer (SIGN)</b>	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results	1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	B	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+	1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	C	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 2++	1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+	2++ High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	✓	Recommended best practice based on the clinical experience of the guideline development group	2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
			2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 Non-analytic studies, E.g. case reports, case series 4 Expert opinion
<b>NICE 2015</b>	No specific grading system provided. Evidence was reviewed and the quality was described in detail for each question posed to be answered in the guideline		
<b>ESHRE</b>	A	Meta-analysis, systematic review or multiple randomized controlled trials (RCTs) (high quality)	
	B	Meta-analysis, systematic review or multiple RCTs (moderate quality) Single RCT, large non-randomized trial, case-control or cohort studies (high quality)	
	C	Single RCT, large non-randomized trial, case-control or cohort studies (moderate quality)	
	D	Non-analytical studies, case reports or case series (high or moderate quality)	
	GPP	Expert opinion	