

## Review article



## Eligibility criteria for Menopausal Hormone Therapy (MHT): a position statement from a consortium of scientific societies for the use of MHT in women with medical conditions. MHT Eligibility Criteria Group

Nicolás Mendoza<sup>a,\*</sup>, Isabel Ramírez<sup>a</sup>, Esther de la Viuda<sup>a</sup>, Pluvio Coronado<sup>a</sup>, Laura Baquedano<sup>a</sup>, Plácido Llanaez<sup>a</sup>, Verónica Nieto<sup>a</sup>, Borja Otero<sup>a</sup>, Sonia Sánchez-Méndez<sup>a</sup>, Visitación Álvarez de Frutos<sup>b</sup>, Leire Andraca<sup>c</sup>, Patricio Barriga<sup>d</sup>, Zully Benítez<sup>e</sup>, Teresa Bombas<sup>d</sup>, M<sup>a</sup>. Jesús Cancelo<sup>f</sup>, Antonio Cano<sup>g</sup>, Camil Castelo Branco<sup>h</sup>, Marta Correa<sup>i</sup>, José Luis Doval<sup>a</sup>, María Fasero<sup>a</sup>, Gabriel Fiol<sup>a</sup>, Nestor C. Garello<sup>j</sup>, Andrea R. Genazzani<sup>h</sup>, Ana Isabel Gómez<sup>k</sup>, M<sup>a</sup>. Ángeles Gómez<sup>a</sup>, Silvia González<sup>a</sup>, Dimitrios G. Goulis<sup>g</sup>, Misericordia Guinot<sup>a</sup>, Luis Rolando Hernández<sup>j</sup>, Sonia Herrero<sup>l</sup>, Eva Iglesias<sup>a</sup>, Ana Rosa Jurado<sup>m</sup>, Iñaki Lete<sup>a</sup>, Daniel Lubián<sup>a</sup>, Milagros Martínez<sup>a</sup>, Aníbal Nieto<sup>a</sup>, Laura Nieto<sup>a</sup>, Santiago Palacios<sup>n</sup>, Milagros Pedreira<sup>o</sup>, Ezequiel Pérez-Campos<sup>a</sup>, María Jesús Plá<sup>p</sup>, Jesús Presa<sup>a</sup>, Francisco Quereda<sup>a</sup>, Miriam Ribes<sup>a</sup>, Pablo Romero<sup>a</sup>, Beatriz Roca<sup>a</sup>, Antonio Sánchez-Capilla<sup>q</sup>, Rafael Sánchez-Borrego<sup>r</sup>, Ana Santaballa<sup>s</sup>, Amparo Santamaría<sup>t</sup>, Tommaso Simoncini<sup>u</sup>, Francisco Tinahones<sup>v</sup>, Joaquín Calaf<sup>a</sup>

<sup>a</sup> Asociación Española para el Estudio de la Menopausia (AEEM), Spain

<sup>b</sup> Sociedad Española de Endocrinología y Nutrición (SEEN), Spain

<sup>c</sup> Sociedad Española de Farmacia Comunitaria (SEFAC), Spain

<sup>d</sup> Red Iberoamericana de Salud Sexual y Reproductiva (REDISSER)

<sup>e</sup> Federación Latino Americana de Sociedades de Climaterio y Menopausia (FLASCYM)

<sup>f</sup> Sociedad Española de Ginecología y Obstetricia (SEGO), Spain

<sup>g</sup> European Menopause and Andropause Society (EMAS)

<sup>h</sup> European Society of Gynecology (ESG)

<sup>i</sup> Sociedad Española de Contracepción (SEC), Spain

<sup>j</sup> Federación Latino-Americana de Sociedades de Obstetricia y Ginecología (FLASOG)

<sup>k</sup> Sociedad Española de Senología y Patología Mamaria (SESPM), Spain

<sup>l</sup> Sociedad Española de Trombosis y Hemostasia (SETH), Spain

<sup>m</sup> Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Spain

<sup>n</sup> International Menopause Society (IMS)

<sup>o</sup> Sociedad Española de Cardiología (SEC), Spain

<sup>p</sup> Sección Ginecología Oncológica de la SEGO, Spain

<sup>q</sup> Sociedad Española de Patología Digestiva (SEPD), Spain

<sup>r</sup> Fundación Española para el Estudio de la Menopausia (FEEM), Spain

<sup>s</sup> Sociedad Española de Oncología Médica (SEOM), Spain

<sup>t</sup> Sociedad Española de Hematología y Hemoterapia (SEHH), Spain

<sup>u</sup> International Society of Gynecological Endocrinology (ISGE)

<sup>v</sup> Sociedad Española de Obesidad (SEED), Spain

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## ABSTRACT

This project aims to develop eligibility criteria for menopausal hormone therapy (MHT). The tool should be similar to those already established for contraception. A consortium of scientific societies coordinated by the Spanish Menopause Society met to formulate recommendations for the use of MHT by women with medical

\* Corresponding author.

E-mail address: [nicomendoza@telefonica.net](mailto:nicomendoza@telefonica.net) (N. Mendoza).

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Eligibility criteria  
Medical conditions

conditions based on the best available evidence. The project was developed in two phases. As a first step, we conducted 14 systematic reviews and 32 meta-analyses on the safety of MHT (in nine areas: age, time of menopause onset, treatment duration, women with thrombotic risk, women with a personal history of cardiovascular disease, women with metabolic syndrome, women with gastrointestinal diseases, survivors of breast cancer or of other cancers, and women who smoke) and on the most relevant pharmacological interactions with MHT. These systematic reviews and meta-analyses helped inform a structured process in which a panel of experts defined the eligibility criteria according to a specific framework, which facilitated the discussion and development process. To unify the proposal, the following eligibility criteria have been defined in accordance with the WHO international nomenclature for the different alternatives for MHT (category 1, no restriction on the use of MHT; category 2, the benefits outweigh the risks; category 3, the risks generally outweigh the benefits; category 4, MHT should not be used). Quality was classified as high, moderate, low or very low, based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias). When no direct evidence was identified, but plausibility, clinical experience or indirect evidence were available, "Expert opinion" was categorized. For the first time, a set of eligibility criteria, based on clinical evidence and developed according to the most rigorous methodological tools, has been defined. This will provide health professionals with a powerful decision-making tool that can be used to manage menopausal symptoms.

## 1. Introduction

The data collected during the last two decades on the effects of menopausal hormone therapy (MHT) could help to provide a safer and more effective treatment of menopause symptoms as well as an improved quality of life [1–2]. Based on all of this information, international societies have concluded that the benefits of MHT outweigh the risks in healthy symptomatic postmenopausal women when MHT is initiated within 10 years of the menopause or when younger than 60 years of age [3,4].

However, there are currently no guidelines available that provide specific recommendations on the prescription of MHT in postmenopausal women with any medical condition. In the absence of reliable information, the fear of aggravation of the pre-existing condition prevents the general practitioner or health care provider from prescribing MHT when symptoms impair quality of life.

In the case of contraceptive methods, there is a globally available document that provides information for this purpose. Thus, the "WHO Medical Eligibility Criteria" classifies the various medical conditions of women into four categories, providing the scientific community with recommendations for the safe use of any contraceptive method [5].

The objective of this study was to create eligibility criteria for the use of MHT similar to those established for contraceptive methods. A consortium of Scientific Societies coordinated by the Spanish Menopause Society (Asociación Española para el Estudio de la Menopausia, AEEM, see Appendix 1) met to define eligibility criteria for the use of THM in women with main medical conditions found in the researched database.

## 2. Methodology

The study was conducted in two phases. As a first step, we conducted a series of systematic reviews on the safety of MHT, addressing nine clinical questions. We then developed a working framework to formulate explicit, reasoned recommendations. The findings of these systematic reviews helped to inform a structured process in which a panel of experts defined the eligibility criteria according to a specific framework, which facilitated the discussion and development process.

The objectives and methodology (Systematic reviews for the definition of MHT eligibility criteria) are described in a previous paper [6].

### 2.1. Evidence synthesis

#### 2.1.1. Definition of clinical questions

We defined a common protocol for conducting a systematic review to respond to eight clinical questions concerning various conditions. The protocol was registered in PROSPERO (registration number CRD42020166658) and in the Open Science Framework platform (DOI 10.17605/OSF.IO/J6WBC). The reviews were conducted according to

standardised criteria [7]. First, members from the expert panel defined the specific clinical questions:

- How safe is MHT according to age, time of menopause onset, and treatment duration?
- How safe is MHT in women with thrombotic risk?
- How safe is MHT in women with a personal history of cardiovascular disease?
- How safe is MHT in women with metabolic syndrome?
- How safe is MHT in women with gastrointestinal diseases?
- How safe is MHT in female survivors of breast cancer?
- How safe is MHT in female survivors of other cancers?
- How safe is MHT in smoking women?
- Which are the most important pharmacological interactions with MHT?

More specifically, these questions focused on the age of the women, the time after menopause at which MHT is prescribed and its duration, along with the risks associated with previous cancers and comorbidities such as endocrine, digestive and cardiovascular diseases.

We additionally explored the impact of hypertension, obesity, migraines, smoking and prothrombotic mutations as additional risk factors to the conditions defined through the clinical questions. Finally, we considered the most common drugs that interact with MHT. The members of the panel — with the support of two experts in evidence synthesis methodology — framed the clinical questions to define the population and sub-groups of interest and to identify the outcomes of interest [8], establishing the inclusion criteria for the systematic reviews.

#### 2.1.2. Inclusion criteria

The systematic reviews included randomized controlled trials, and related extension studies or follow-up reports. Additionally, we included observational studies (with special interest in population-based cohorts or large case-control studies), including a control group of non-users. Studies considered eligible if they included menopausal women of any age receiving MHT, and affected by any of the conditions of interest defined in the clinical questions.

We considered studies that evaluate any MHT regimen (oestrogens alone in hysterectomized women or combined with a progestogen, tibolone or tissue-selective oestrogen complex) with any route of administration (oral, transdermal, vaginal or intra-nasal). The impact of MHT was compared with placebo or non-treatment controls. We defined a range of specific clinical outcomes of interest according to the scope of each clinical question (e.g., recurrence of disease for cancer survivors or new thromboembolic events in women with cardiovascular or thrombotic risk).

### 2.1.3. Searches and eligibility

We conducted exhaustive literature searches in the following databases: MEDLINE (via PubMed), The Cochrane Library (CENTRAL), and EMBASE (via embase.com), from their inception until the most recent date. We designed a search strategy that is tailored to the requirements of each database, which included a combination of controlled vocabulary and search terms related to each clinical question and the associated inclusion criteria. [Appendix 2](#) displays an exploratory search strategy for MEDLINE. When necessary, we used validated filters to retrieve the appropriate study designs.

Additionally, we checked the reference lists of relevant studies or reviews identified and map any secondary publications from large studies in the field (e.g., the Women's health initiative trial for most of the clinical questions or the Estrogen in Venous Thromboembolism Trial to assess safety in women with a history of thromboembolic disease). Initially, no restrictions were applied in terms of language, date, or status of publication.

Two independent researchers screened the references yielded by the search to reach an agreement on the inclusion of studies for each review, according to the criteria defined for each clinical question. We involved a member of the expert panel to resolve any discrepancies. The panel members were informed about this process in order to evaluate the suitability of the included studies and suggested additional studies if relevant articles were omitted.

### 2.1.4. Data extraction and risk of bias assessment

The Panel, which comprised the authors of the study, reviewed the scientific literature according to a protocol following methodological guidelines from the Cochrane collaboration [7] and reported its findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8]. For observational studies, we adapted the ROBINS I tool, focusing on the evaluation of the impact of the confounding variables, selection bias, outcome measures, and attrition [9].

We made explicit judgements on the certainty of the evidence for each outcome of interest according to GRADE criteria [10]. Quality was classified as high (A), moderate (B), low (C) or very low (D), based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias). In those systematic reviews where no direct evidence was identified, but plausibility was considered to exist or clinical experience or publications with indirect evidence were available, consensus decisions were made by the panel and categorised as "Expert opinion".

### 2.1.5. Data synthesis

We described the synthesis of the evidence for each clinical question in reports that followed the PRISMA guidelines. We developed a narrative synthesis of the findings and effect estimates from the included studies focusing on the outcomes of interest, to explore the association between the MHT and the outcomes of interest.

When appropriated, pooled analyses were conducted using the Mantel-Haenszel method and the random effects model included within the RevMan software statistical package (v 5.3.5) [11].

We reported explicit judgements to rate the quality of the evidence for each outcome. The results and quality assessment of each outcome of interest were presented in the summary of findings tables [10–12].

## 2.2. Evidence to decision framework and eligibility criteria

In order to formulate the recommendations in an explicit and reasoned manner, we used an evidence to decision (EtD) framework to inform the Panel of the most relevant aspects necessary for taking decisions and thus making them easy to justify [13].

To produce a ranking of MHT eligibility criteria, The Panel integrated the findings of the reviews according to a structured framework that considered the magnitude of the MHT effects for each outcome and

population of interest, the certainty ratings of the evidence, and data from other sources of evidence.

To unify the proposal, the following eligibility criteria have been defined in accordance with the WHO international nomenclature:

- Category 1: No restriction on the use of MHT
- Category 2: The benefits outweigh the risks.
- Category 3: The risks generally outweigh the benefits.
- Category 4: MHT Should not be used

### 2.3. Exceptional situations

The term MHT embraces a wide variety of preparations (synthetic and natural) used with different compositions, routes of administration, and dosage. This heterogeneity implies different effects of the interaction with the medical conditions analysed. The wide range of combinations adds variability to drug interactions or medical conditions. For this reason, we mentioned the peculiarities regarding routes or doses within each section. Moreover, in some therapeutic groups, the eligibility assignment may include more than one number due to differences, explained in the footnote. We have explicitly analysed some treatment regimens targeting steroid receptors and not being ovarian steroids.

The TSEC complex is a drug combination of oestrogen and selective in the SERM group since it is associated with MHT.

Tibolone, despite being a progestogen as a molecule, has its own column due to its particular characteristics, clinical effects comparable to combined MHT, and evidence of influence on medical conditions and possible interactions has its specific molecule.

Quality evidence on the effects of vaginal MHT is scarce. Pharmacodynamic studies show a lack of absorption and systemic effects after two weeks of use. Clinical experience supports the absence of effects or drug-drug interactions and influences on medical conditions.

Beyond this article, the reports of the groups analysing the evidence gathered for each question will be published in a complete document and, when appropriated, in specific papers.

## 3. Results

### 3.1. Systematic reviews and meta-analyses

After the first search, we identified 8657 articles fulfilling the search strategy terms. A thorough analysis selecting only the prospective studies, peer-reviewed and with one of the arms being any of the forms of MHT, were selected 119 pieces of evidence for evaluation [14–249] (see [Fig. 1](#) and [Appendix 3](#)).

A total of 14 systematic reviews were conducted (three for age, three for thrombosis, two for CVD, one for digestive issues, one for metabolic syndrome, two for breast cancer, one for other cancers, and one for tobacco). Moreover, a specific one reviews reference to address the question of drug interactions.

In addition, 32 meta-analyses were conducted: seven for CVD, three for metabolic syndrome, nine for breast cancer, and thirteen for other cancers.

### 3.2. MHT eligibility criteria

In [Tables 1 to 4](#), we present the recommendations of the different analysis groups after being reviewed by internal and external committees.

They show the results of analysing 252 potential scenarios combining clinical conditions and MHT alternatives. We have identified 8(3,2%) combinations rated with a 4. The group considered that the prescription of any of the forms of MHT should be avoided.

In 28 scenarios (11,1%), the evaluating group considered that the risks outweighed the benefits and rated the situation 3. Furthermore, in 21 potential clinical situations (8,3%), the rating is between 2 and 3

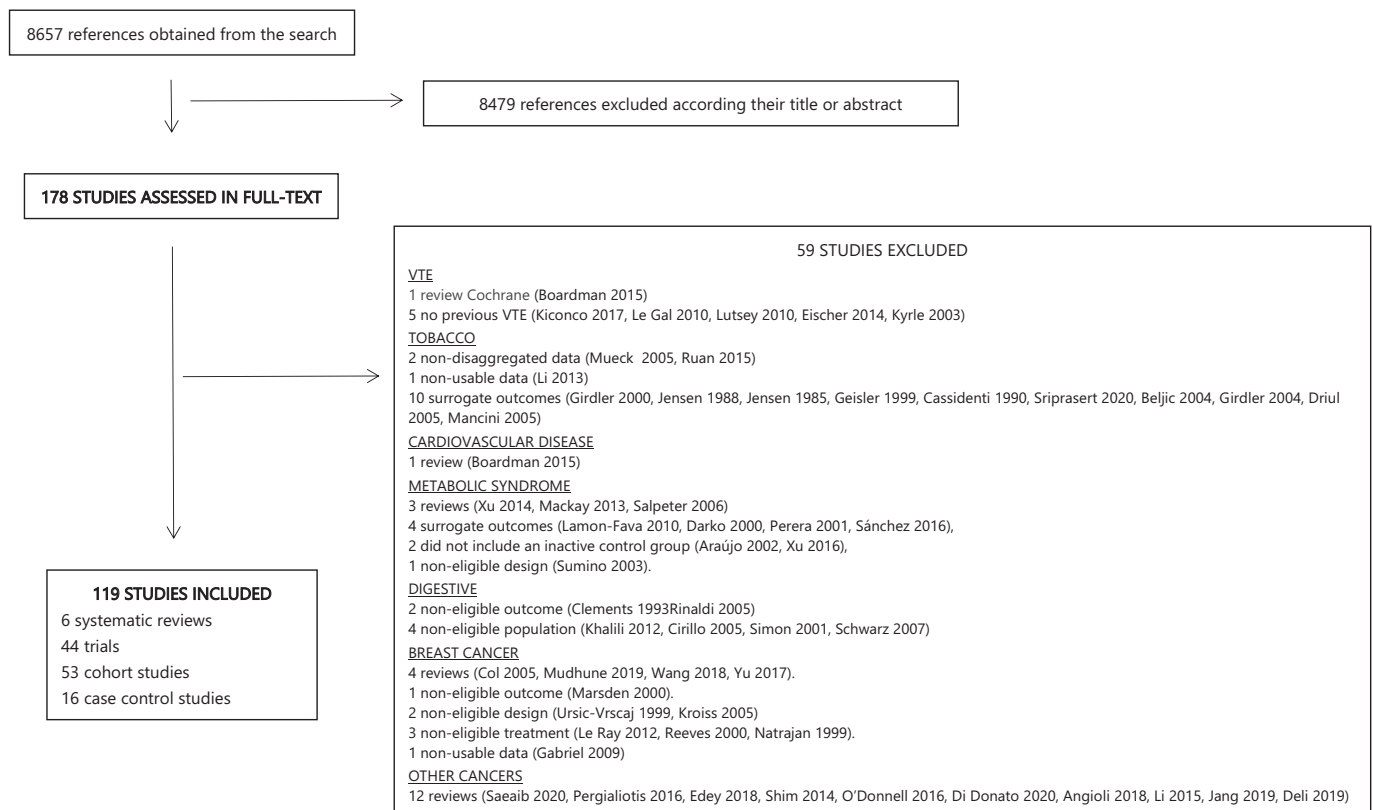


Fig. 1. PRISMA flowchart for the clinical questions defined by the MHT Eligibility Criteria Group

Table 1  
Age, duration and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT <sup>1</sup>	Clarifications
Age	Duration	Oral	Trsd	Oral	Trsd			
<40 <sup>2,*</sup>	<5 years	1C	1	1C	1C	NA	1	* For tibolone, the available evidence is for safety with respect to the risk of VT/PE and breast cancer (>50 years). There is no evidence for cardiovascular risk.
	≥5 years	1C	1C	1C	1C	NA	1	
40–44 <sup>3,*</sup>	<5 years	2C	1C	2C	1C	2C**	1	** The available evidence is low due to the limited number of cases included in the studies. The clear benefit of using MHT in women under 50 years of age should be considered.
	≥5 years	2C	2C	2C	2C	2C**	1	
45–49 <sup>3,*</sup>	<5 years	2C	2C	2C	1C	2C**	1	*** MHT Continuation (Category 2)/MHT initiation >10 years after menopause (Category 3)
	≥5 years	2C	2C	2C	2C	2C**	1	
50–59	<5 years	2B	2B	2B	2B	2C	1	
						(<55) 1C		
						(>55) 2C	1	
60–69	<5 years	2/ 3B***	2/ 3B***	2/ 3B***	2/ 3B***	2C	1	
	≥5 years	2/ 3***	2/ 3***	2/ 3***	2/ 3***	2C	1	
						(<55) 1C		
>70	<5 years	3D	3D	3D	3D	2C	1	
	≥5 years	3D	3D	3D	3D	3C	1	

MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; Trsd = transdermal; VT/PE: venous thrombosis/pulmonary embolism

<sup>1</sup> For easy to understand, no quality studies address the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience

<sup>2</sup> The group of menopause under 40 is defined now by the term premature ovarian insufficiency (POI). Guidelines suggest that MHT should be continued until the average age of menopause (age 50–51 years) to prevent premature bone loss, coronary heart disease, stroke, and an increased risk of dementia. At that point, if MHT is stopped and menopausal symptoms are moderate to severe, the same discussion of potential risks and benefits of MHT should take place.

<sup>3</sup> If hormonal contraception is needed, it is recommended to maintain it until age 50.

according to specified circumstances.

(65.1%).

Consequently, MHT has been safe or with the benefits being higher than the potential threats (rated 1 or 2) in 164 potential combinations

**Table 2**  
Medical conditions and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT <sup>a</sup>	Clarifications
		Oral	Trsd	Oral	Trsd			
Thrombotic risk	VT/PE without anticoagulation	4B	3C	4B	3C	NA	1	* If necessary, the transdermal MHT is preferred (expert opinion).
	VT/PE with anticoagulation		3D*		3D*			
	Asymptomatic thrombophilia	4B	2B	3B	2B	NA	1	
Neurological disorders	Migraine Without aura	2C*	2	2	2	NA	1	Continuous administration of MHT can avoid the estrogen withdrawal migraine * The administration of an antiplatelet agent may be considered (expert opinion). O (Onset): Migraine occurs before MHT). C (continuation): migraine occurs after MHT).
	Migraine With aura	3D*	2C (O)/3C* (C)	3D*	2C (O)/3C* (C)	2C (O)/3C*(C)	1	
Cardiovascular disease	Tension headache	1B	1B	NA	NA	1	1	*Exception: young women whose stroke is not due to arteriosclerosis, or after haemorrhagic strokes with a normal coronary history and without other associated RF (diabetes mellitus, smoking, hypertension or dyslipidaemia). Expert opinion. * No ischaemic cause of AMI or other RF (Expert opinion). ** Those who have undergone coronary artery bypass grafting with saphenous vein grafting have a better prognosis if they are under MHT with oestrogen alone at the time of revascularisation. Therefore, in these patients it could be recommended to maintain MHT. *ischaemic cause or with other RFs (Expert opinion).
	Stroke	3A	3A/D2*	3A	3A/2D*	NA	1	
	Non-fatal AMI	3A/2D*	3A/2D*	3A/2C**	3A/2C***	NA	1	
	Angina	2A/3D*	2A/3D*	2A/3D+	2A/3D*	NA	1	
Smoking	High blood pressure	2B/1A***	2B	2B/1B****	2B	2B	1	*** Combination of oestradiol + drospirenone. **** Combination of oestradiol + norethisterone.
	Diabetes mellitus	3C	2C	3C	2C	NA	1	
Metabolic disorders related to the metabolic syndrome	Hypercholesterolemia	1B	1D	2C	1D	NA	1	* No data in women with BMI >35. * Assess additional thrombotic risk factors.
	Hypercholesterolemia and diabetes	1D	1D	1D	1D	NA	1	
Digestive Diseases	BMI 25-30 kg/m2	1C	1C	1C	1C	NA	1	* No data in women with BMI >35. * Assess additional thrombotic risk factors.
	BMI >30 kg/m2*	2B	1B	2B	1B	NA	1	
	Inflammatory bowel disease*	3B	2B	3B	2B	NA	1	
	History of hepatitis C	2D	1D	2D	1D	NA	1	
	Acute hepatitis	2C	2C	2C	2C	NA	1	
Cirrhosis		4/3D**	4/3D**	4/2D**	4/2D**	NA	1	**Depending on the severity of the condition.
		NA*	NA*	NA*	NA*	NA*	1	* Not because of the preparation but because of liver damage. Category 4 would apply (expert opinion).

AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; HC = hormonal contraceptives; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal; VT/PE: venous thrombosis/pulmonary embolism

<sup>a</sup> For easy to understand, no quality studies address the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience.

#### 4. Discussion

The objective of this project was to create a set of eligibility criteria for the use of MHT, similar to those established for contraceptive methods. A consortium of scientific societies coordinated by AEEM met to develop a set of guidelines on the use of MHT in women depending on age and duration of use or with various medical conditions based on the best available evidence.

MHT is underused according to the difference between the published incidence of severe symptoms and the estimated number of users. A relevant driver for this underuse is the fear from both women and prescribers of inducing more harm than benefit. Excessive precaution is even more critical when dealing with women presenting additional morbidities. Moreover, quality evidence exploring the effects of MHT on pathological situations is scarce. To our knowledge, a tool that assists clinicians in the decision-making process of MHT prescribing in these situations is unavailable [250–252].

A group of experienced clinicians selected by the Spanish Menopause Society (AEEM) have identified nine frequent clinical scenarios that

could make the counselling process difficult. After analysing the evidence available for any scenario combined with any MHT type, we have identified 36 out of 252 (14,3%) combinations where these treatments should be avoided. A systematic review identified 236 papers contributing to understanding the potential effects of any MHT in these patients.

These findings suggest a treatment alternative for severely symptomatic women where the benefits outweigh the risks in most clinical scenarios. With this information, health care providers counselling postmenopausal women will have a readily available tool to identify potentially risky situations. Consequently, the number of women accessing a needed MHT should increase.

The most critical limitation found during the development of the tool has been the limited number of quality studies exploring specifically the interaction between diseases or situations and MHT alternatives. No studies address specific clinical conditions for some approaches (route, presentation or molecule) and vice versa. In some of these cases, the final decision has been taken based on the best available evidence that was, unfortunately, expert opinion based on the data obtained in healthy

**Table 3**  
Cancer and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT	Clarifications
		Oral	Trsd	Oral	Trsd			
Breast cancer	BCS (HR-)	2B	2B	2B	2B	2B	2D*	* Recommendation based on the opinion of regulatory agencies.
	BCS (HR+)	3C	3C	3C	3C	4A	2D*	* Recommendation based on the opinion of regulatory agencies.
	BRCA carrier1	2C	2C	2C	2C	NA	1D	
	BRCA2 carrier*	2D*	2D*	2D*	2D*	NA	1D	* BRCA1 extrapolation (expert opinion).
Gynaecological cancers	Ovarian cancer	1B*	1B*	1B*	1B*	1B*	1D	* Longer survival and lower recurrence, particularly in those under 55 years of age. There does not appear to be a difference according to type of MHT or route of administration. There is no literature that supports or excludes MHT for non-epithelial tumours.
	Endometrial cancer	2C*	2C*	2C*	2C*	2C*	1D	* No differences in DFS (less recurrence with combined MHT than with oestrogen-only MHT).
	Cervical cancer	2C*	2C*	2C*	2C*	2C*	1D	*No difference in survival or DFS. Little evidence.
Other cancers	Colon cancer	1C*	1C*	1C*	1C*	NA	1D	* No differences between different forms of MHT are evaluated. ** Seems to show better results with oestrogens-only MHT.
	Lung cancer	2C*	2C*	2C*	2C*	NA	1D	* No differences between different forms of MHT are assessed. Smoking increases the risk.
	Melanoma	2C*	2C*	2C*	2C*	NA	1D	* Only one cohort study with a large 10-year follow-up.

BCS = Breast cancer survivors; DFS = disease-free survival; HR = hormonal receptors; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal.

women.

A relevant strength of the tool is the quality of the review process by identifying studies, evaluating their quality, and the degree of recommendation that could be drawn from them. Throughout the process, a rigorous and systematic methodology has been applied in accordance with internationally accepted guidelines. The quality of the tool is enhanced by the wide external and internal reviews. The process involved up to 21 members of Spanish and international scientific societies related to the diseases explored in the study. Their comments and recommendations have been either discussed or included in the tool.

We hope that a widespread diffusion of this decision tool will increase the use of MHT in severely symptomatic postmenopausal women affected by frequent comorbidities. The tool has to be updated as new non-analysed scenarios are identified.

Our report has undoubtedly identified some important areas for improvement for future research. We expect that our findings will contribute to the development of studies that continue to analyse the safety and efficacy of MHT in treating menopausal symptoms in women with the medical conditions described. More extensive RCTs should be conducted, and over a longer follow-up period, to evaluate the various MHT strategies.

**Contributors**

Nicolás Mendoza contributed to conception and design of the idea, coordination and preparation of manuscript, manuscript editing, and was a member of the Expert Panel.

Isabel Ramírez contributed to conception and design of the idea, coordination and preparation of manuscript, and was a member of the Expert Panel.

Esther de la Viuda contributed to conception and design of the idea, coordination and preparation of manuscript, and was a member of the Expert Panel.

Pluvio Coronado coordination and preparation of manuscript.

Laura Baquedano coordination and preparation of manuscript, and was a member of the Expert Panel.

Plácido Llana coordination and preparation of manuscript, and was a member of the Expert Panel.

Verónica Nieto coordination and preparation of manuscript.

Borja Otero coordination and preparation of manuscript, and was a member of the Expert Panel.

Sonia Sánchez-Méndez coordination and preparation of manuscript, and was a member of the Expert Panel.

Visitación Álvarez de Frutos was a member of the Expert Panel. Leire Andraca was a member of the Expert Panel. Patricio Barriga contributed to external review. Zully Benítez contributed to external review. Teresa Bombas contributed to external review. M<sup>o</sup> Jesús Cancelo contributed to external review. Antonio Cano contributed to external review. Camil Castelo Branco was a member of the Expert Panel. Marta Correa was a member of the Expert Panel. José Luis Doval was a member of the Expert Panel. María Fasero was a member of the Expert Panel. Gabriel Fiol was a member of the Expert Panel. Nestor C Garello contributed to external review. Andrea R Genazzani contributed to external review. Ana Isabel Gómez was a member of the Expert Panel. M<sup>o</sup> Ángeles Gómez was a member of the Expert Panel. Silvia González was a member of the Expert Panel. Dimitrios G Goulis contributed to external review. Misericordia Guinot was a member of the Expert Panel. Luis Rolando Hernández contributed to external review. Sonia Herrero was a member of the Expert Panel. Eva Iglesias was a member of the Expert Panel. Ana Rosa Jurado was a member of the Expert Panel and contributed to external review..

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**Table 4**  
Drug interactions and MHT eligibility criteria<sup>a</sup>.

Drug	Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT	Clarifications
	Oral	Trsd	Oral	Trsd			
Antihypertensives*	1**/ 2***	1	2***	1	2***	1	* Despite the lack of possible interaction studies, the evidence of extensive co-use without reporting associated problems is considered sufficiently relevant. **With drospirenone. *** In some patients, probably with certain idiosyncrasies, oral MHT may alter BP control and require dose adjustment and confirmation that this is resolved.
Statins*	1/2**	1 ***	1/ 2**	1 ***	1/2**	1	*same comment as with antihypertensives. ** Oral MHT tends to increase triglycerides, total cholesterol and LDL-cholesterol, and to increase HDL-cholesterol. No interaction, but consider according to patient profile. *** Transdermal MHT modifies lipid profile less. No interaction but consider if there is indication or loss of desirable benefit according to patient profile.
Anxiolytic/hypnotics	1	1	1	1	1/2*	1	* Midazolam.
Analgesics/anti-inflammatories	1	1	1	1	1	1	
Antidepressants	1	1	1	1	1	1	
Aromatase inhibitors	4	4	4	4	4	1	
Oral anti-diabetics	1	1	1	1	1	1	
Insulin	1	1	1	1	1	1	
Thyroid hormones*	1	1	1	1	1	1	* Assess dose adjustment (little clinical relevance)
Bronchodilators	1*	1	1*	1	1*	1	* With oral theophylline adjust dose.
Anticoagulants	1/2*	1	1/2*	1	2*	1	* In some women (particularly at baseline), adjustment of the warfarin anticoagulant dose, discontinuation of MHT, or change of administration route may be required
SERMS	4	4	4	4	4		
Corticoids	2	2	2	2	2	1	
Antiepileptics *	4	3	4	3	4	1	* Most antiepileptic drugs are potent enzyme inducers, and could thus reduce oestrogenic effectiveness. Oral MHT may reduce the effect of the antiepileptic drug by interfering with its metabolism.
Enzyme inhibitor antibiotics (rifampicin/rifbutin)	2	2	2	2	2	1	
Antineoplastics	4	4	4	4	4	1	
Immunosuppressors	3	3	3	3	3	1	
Oral antifungals	1/2*	1	1/2*	1	1/2*	1	*In chronic treatments.
Antiretrovirals	1/2*	1/ 2*	1/2*	1/ 2*	1/2*	1	Tipranavir) are enzyme inducers and reduce the oestrogenic effect; but non-nucleoside reverse transcriptase inhibitors (Efavirenz, Nivirapine) are enzyme inducers that do not reduce the oestrogenic effect.
Dopaminergics	2	2	2	2	2	1	In the rare cases where these substances have to be administered in postmenopausal women with prolactinoma, MHT does not interfere with the tumour control effect.
Litolitics*	3	2	3	2	3	1	* Decreased litholytic effect and increased hepatic cholesterol have been reported with HC, which could perhaps occur with oral MHT.
Neurostimulants	2	2	2	2	2	1	
Antithyroid	2	2	2	2	2	1	
Antipsychotics *	2/3*	2/ 3*	1	1	1	1	* Some studies have reported progestogen interaction for aripiprazole and pimozide.

HC = hormonal contraceptives; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal; SERM: selective estrogen receptor modulators

<sup>a</sup> For easy to understand, no quality studies address the interactions between unfrequent medications and MHT. Similarly happens with the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience.

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### Appendix 1. Consortium of scientific societies

Asociación Española para el Estudio de la Menopausia (AEEM)  
 European Menopause and Andropause Society (EMAS)  
 European Society of Gynecology (ESG)  
 Federación Latinoamericana de Sociedades de Obstetricia y Ginecología (FLASOG)  
 Federación Latinoamericana de Sociedades de Climaterio y Menopausia (FLASCYM)  
 Fundación Española para el Estudio de la Menopausia (FEEM)  
 International Menopause Society (IMS)  
 International Society of Gynecological Endocrinology (ISGE)  
 Red Iberoamericana de Salud Sexual y Reproductiva (REDISSER)  
 Sección de Ginecología Oncológica de la SEGO (SGOSEGO)  
 Sociedad Española de Cardiología (SEC)  
 Sociedad Española de Contracepción (SEC)  
 Sociedad Española de endocrinología y nutrición (SEEN)  
 Sociedad Española de Farmacia Comunitaria (SEFAC)  
 Sociedad Española de Ginecología y Obstetricia (SEGO)  
 Sociedad Española de Hematología y Hemoterapia (SEHH)  
 Sociedad Española de Médicos de Atención Primaria (SEMERGEN)  
 Sociedad Española de Oncología Médica (SEOM)  
 Sociedad Española de Patología Digestiva (SEPD)  
 Sociedad Española de Senología y Patología Mamaria (SESPM)  
 Sociedad Española de Trombosis y Hemostasia (SETH)  
 Sociedad Española para el Estudio de la Obesidad (SEEDO)

### Appendix 2. Exploratory search designed for medline (accessed through PubMed)

("Hormone Replacement Therapy"[MeSH Major Topic] OR "hormone therapy"[Title] OR ("hormone\*" [Title] AND "therapy"[Title] AND "menopause\*" [Title]) OR "menopausal hormone therapy"[Title/Abstract] OR "Hormone Replacement Therapy"[Title/Abstract])

### Appendix 3. Included studies by clinical question

#### Included studies by clinical question

AGE	6 reviews or pooled data sets (CGHFBC 2019, CGESOC 2015, Nudy 2019, Kim 2020, Oliver-Williams 2019, Zhu 2019) 4 trials (Chlebowski 2010, Anderson 2012, Manson 2013, Manson 2017)
VTE	1 case control (Vinogradova 2020 )

(continued on next page)



(continued)

Included studies by clinical question	
	7 trials (Høibraaten 2001, Herrington 2002, Cushman 2004, EVTET 2000, Nappi 2001, Facchinetti 2002, Nappi 2006) 3 cohorts (Olié 2011, Rossouw 2002, Li 2015) 4 case control (Lowe 2000, Rosendaal 2002, Straczek 2005, Douketis 2010)
CARDIOVASCULAR DISEASE	9 trials (EAGAR 2006, ERA 2000, ESPRIT 2002, HERS I 1998, PHASE 2002, WAVE 2002, WELL-HART 2003, WEST 2001, WHISP 2006) 7 cohorts (Alexander 2001, Angeja 2001, Anveden 2015, Apostolakis 2014, Bretler 2012, Grodstein 2001, Khan 2000)
TOBACCO	2 case control (Lindenfeld 2003, Nussmeier 2002) 2 cohorts (Malek 2019, Wilson 1985)
METABOLIC SYNDROME	1 case control (Mann 1994) 16 trials (Mosnier–Pudar 1991, Brussaard 1997, Cornu 2000, Sutherland 2001, Kanaya 2003, McKenzie 2003, Howard 2004, Scott 2004, Kernohan 2007, Andersson 1997, Thunell 2006, Samaras 1999, Friday 2001, Manning 2001, Manwaring 2000, Osmanağaoglu 2005).
–	7 cohorts (Ferrara 2001, Ferrara 2003, Newton 2003, Kim 2019, Kane 2008, Di Martino 2004, Codes 2007)
DIGESTIVE DISEASES	4 case control (Gami 2003, Cushman 2004, Canonico 2006, Vinogradova 2019)
BREAST CANCER	2 cross sectional (Crespo 2002, Sites 2001) 3 trials (Stockholm, HABITS, LIBERATE) 11 cohorts (Marttunen 2001, Vassilopoulou 2002, Decker 2003, Kotsopoulos 2018, Durna 2002, O’Meara 2001, Dew 1998, DiSaia 2000, Beckman 2001, DiSaia 1996, Rebbeck 2005) 2 case control (Eisen 2008, Kotsopoulos 2016)
OTHER CANCERS	5 trials (Eeles 2015, Li 2012, Guidozzi 1999, Barakat 2006, Ploch 1987) 23 cohorts (Eeles 1991, Mascarenhas 2006, Ursic-Vrscaj 2001, Wen 2013, Power 2016, Zhang 2016, Ayhan 2006, Suriano 2001, Arteaga-Gómez 2011, Creasman 1986, Lee 1990, Chapman 1996, Lim 2018, Cho 2019, Slattery 1999, Mandelson 2003, Chan 2006, Arem 2015, Ji 2018, Ayeni 2009, Huang 2009, Clague 2014, MacKie 2004)

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