Appendix 1. Key Points Summary of the Principles of Prescribing Menopause Hormone Therapy (MHT) – the 5Ws

1) **Who is MHT for?**
   - Usual indications for MHT
     - Distressing vasomotor (VMS) and vulvovaginal atrophy/ genitourinary syndrome of menopause (VVA/GSM) symptoms
     - Osteoporosis prevention (first line in some countries, second line in others)
   - Asymptomatic women
     - MHT is primarily indicated for symptomatic women
     - MHT should not be regarded as an 'elixir of youth'
     - MHT is not currently indicated for primary prevention of cardiovascular disease or dementia in women at usual age of menopause but is important preventive therapy for women with primary ovarian insufficiency (POI)/ early menopause, even if asymptomatic
   - High-risk women
     - Careful counseling of benefit–risk balance required as with any other medication
     - Definition of 'acceptable risk' will vary – personalization of prescribing required
     - Ongoing development of medical eligibility criteria will be useful (as with contraception)
2) **What types and doses of MHT?**
   - Type of estrogen
     - There is no evidence that replicating the precise ratio of the four human estrogens (estrone, estradiol, estriol, estetrol) is required
     - Most types of estrogen will alleviate VMS and VVA/GSM if used in sufficient doses
     - Despite biological differences between estrogen types in MHT there is little evidence of clinically significant differences in efficacy and safety
     - Route of delivery (i.e. oral versus non-oral) has cardiometabolic significance (e.g. no venous thromboembolism [VTE] risk with transdermal estrogen)
     - Healthy women at usual age of menopause can have oral MHT if they prefer, or if they cannot absorb or are allergic to transdermal estrogen
   - Type of progestogen
     - Primary indication for progestogens in MHT is to prevent endometrial hyperplasia/cancer
     - Most progestogens achieve this if used in a sufficient dose/duration
     - There are differences in tolerance and safety of progestogens that should be considered when prescribing MHT
     - Body-identical progesterone and body similar progestogens (e.g. dydrogesterone) have less adverse impact on cardiometabolic and breast risk markers than androgenic progestogens
   - Doses of estrogen and progestogen
     - Prescribing of MHT should be at minimum fully effective doses, to achieve maximum benefits with minimal adverse effects
     - If the dose of estrogen is increased in non-fixed dose MHT formulations, the dose of progestogen should also be increased to maintain adequate endometrial protection
     - In women with progestogen intolerance, lower dose and duration may be required – endometrial surveillance is mandatory with ultrasound ± hysteroscopy ± endometrial biopsy
     - Other options (may be off license/unavailable in some countries) include vaginal progesterone, intrauterine levonorgestrel and oral tissue selective estrogen complex (TSEC) (conjugated equine estrogens [CEE]/ bazedoxifene)
   - Monitoring of MHT
     - Routine hormone profiles are not required to initiate or monitor MHT in women at the usual age of menopause
     - Hormonal profiles may be useful in the following circumstances, especially if a regimen change has already been attempted:
       - Inadequate symptom relief after 12 weeks of com- mencing/switching MHt
       - Persistent adverse effects after 12 weeks of commencing/switching MHT
       - Use of MHT in POI/early menopause especially if efficacy issues/adverse effects, or concern about osteopenia/osteoporosis
       - NB: estradiol levels are most representative of effect on transdermal estrogen therapy, measured by mass spectrometry techniques where available
   - Compounded bioidentical hormone therapy
     - Custom compounded bioidentical hormone therapy is not recommended because of concerns about regulation, rigorous safety and efficacy testing, batch standardization and purity measures
     - Potential benefits of compounded bioidentical hormone therapy can be achieved with conventionally regulated body-identical MHT which has been rigorously tested for efficacy and safety
   - Testosterone
     - Testosterone is an important female hormone the levels of which naturally decline through a woman's life course
     - The primary indication for testosterone replacement in women is hypoactive sexual desire disorder (HSDD) – distressing low libido
     - Benefits for other symptoms (e.g. cognition, mood) are not established based on current trial data and should not be a primary indication for prescribing
     - A biopsychosocial approach should be followed for diagnosis of HSDD and prescribing according to the global consensus statement
     - Testosterone preparations remain off license for women in most countries, requiring down-titration of male preparations such as gels (typically 1/10th of male dose)
3) **When should MHT be started and stopped?**
   - Premature ovarian insufficiency/early menopause
     - Hormone therapy (MHT or combined oral contraceptives [COCS]) should be commenced as early as possible

following diagnosis of POI/early menopause unless contraindicated
- Early institution of treatment restores quality of life and reduces the risk of long-term health risks (osteoporosis/cardiovascular disease/dementia)
- Treatment should be continued at least until the usual age of menopause and personalized continuation of MHT considered after this based on benefit–risk assessment

◦ Premenopause/perimenopause
- MHT is currently indicated for women in menopause/late perimenopause
- Menopause-associated symptoms often commence in pre-menopause or early perimenopause
- MHT can be used off-label in these women but there may be a higher incidence of adverse effects due to intermit- tent endogenous estrogen production
- COCS can be used in women who do not have contraindications other than age; newer estradiol and estetrol COCS may have less VTE risk
- Research of novel treatment approaches in premenopause/perimenopause is urgently required

◦ Older postmenopausal women (≥ 60 years)
- Routine initiation of MHT from age 60 years onwards is not recommended due to potentially increased risks (e.g. VTE with oral MHT, stroke)
- Use of MHT to treat/prevent osteoporosis in women ≥ 60 years is not recommended as a first-line option
- Personalized prescribing based on the benefit–risk assessment is acceptable, especially in women with persistent VMS
- Treatment of vvA/GSM symptoms with topical estrogen is recommended in this age group and is not contraindicated

◦ When should MHT be stopped
- Arbitrary limits (e.g. 5 years) should not be placed on duration of MHT use
- A personalized approach should be employed, empowering women to make an evidence based individual decision
- Ongoing use of MHT rather than initiation of MHT in women ≥ 60 years may be associated with a more favorable risk–benefit profile for cardiovascular/VTE events

4) **<u>Why</u> is MHT important?**

◦ Is menopause being over-medicalized?
- Menopause does not necessarily require treatment beyond optimization of lifestyle, diet, exercise, etc.
- However, distressing menopause-associated symptoms and risks should be proactively identified and addressed by healthcare providers
- Treatment with MHT and medicinal alternatives should always be underpinned by health optimization measures and talking therapies if indicated
- Provision of a routine 'menopause check' globally could help to reduce suffering and reduce the incidence of non-communicable diseases by identifying problems early through screening, especially as VMS are linked with an increased risk of cardiovascular disease
- The vision of the international Menopause Society (IMS) is that all women across the world will have easy and equitable access to evidence-based knowledge and health care, empowering them to make fully informed mid-life health choices

◦ Role of non-hormonal options
- The wider the armamentarium of treatment options, the easier it is to individualize management of menopause
- Women choosing not to use hormone therapies or who have insufficient relief of symptoms/persistent symptoms into later life/adverse effects/contraindications to MHT should be able to choose evidence-based non-hormonal options
- Selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs) should not be used routinely to treat VMS in women who do not have contraindications to MHT
- Access to talking therapies, for example cognitive behavioral therapy/hypnotherapy, needs to be improved in most countries
- Ongoing development of, and access to, non-hormonal options with an indication for VMS, for example neurokinin (NK) receptor antagonists, is imperative to widen therapeutic choices

◦ Therapeutic areas of unmet need
- Areas of unmet need remain despite improved awareness of menopause. These include:
- VVA/GSM – symptoms affect more than 50% of the post-menopause population and yet only the minority receive topical MHT, leaving women 'suffering in silence'
- POi/early menopause – higher prevalence than originally thought (POI up to 4% especially in low and middle-income countries [IMICs]); many still present too late, or not at all, by which stage preventable complications have arisen and cause more of a problem
- Perimenopause – symptoms are common and distressing, but hormone therapy is more challenging due to fluctuating hormone levels, and is therefore not attempted even though it could be
  - Iatrogenic menopause due to:
    - Benign causes/non-hormone-dependent cancer – MHT can usually be prescribed but is often neglected resulting in suffering and needless non-communicable dis- eases (NCDs)
    - Hormone-dependent cancer – benefit–risk balance of MHT and non-hormonal options should be discussed proactively

5) **<u>Where</u> can MHT be accessed?**

◦ Access to MHT in low and middle-income countries
- Women in many countries, especially in IMICs, have little or no access to MHT and alternative options for menopause management – this situation needs to improve
- National and international menopause societies play a vital role in improving awareness and providing education about menopause and MHT – this can

be achieved through translated guidelines/online educational tools/apps/Artificial intelligence (Ai), etc.

- Improved menopause healthcare provision is essential in view of global aging and the pandemic of non-communicable diseases in this United Nations Decade of Healthy Aging

◦ Impact of 'social and political influencers' on MHT

- Misinformation and disinformation in social and other media can lead to confusion and disempowerment of women about the menopause and MHT
- Expectations about the potential benefits and risks of MHT often do not match reality and can lead to disappointment for MHT users
- Governments, healthcare professionals (HCPs) and society in general have a duty of care to fully inform women about menopause to empower them to make a choice that is right for them
- Appropriate menopause/MHT advice will have societal as well as personal benefits through:
    - Reduction of the societal healthcare burden
    - Improved efficiency and productivity in the workplace

Notes:

(1) Please see full manuscript for greater detail regarding MHT types, doses, regimens, references, etc.

(2) Link to iMS (https://imsociety.org) and Menopause info (https:// menopauseinfo.org) websites.

(3) Progestogens = progesterone and synthetic progestins.