

## ORIGINAL STUDY

# A core outcome set for genitourinary symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative

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### Abstract

**Objective:** Genitourinary symptoms, such as vaginal dryness and pain with sex, are commonly experienced by postmenopausal women. Comparing treatments for these genitourinary symptoms are restricted by the use of different outcome measures in clinical trials and the omission of outcomes, which may be relevant to women. The aim of this project was to develop a Core Outcome Set (COS) to be reported in clinical trials of treatments for genitourinary symptoms associated with menopause.

**Methods:** We performed a systematic review of randomized controlled trials of treatments for genitourinary symptoms associated with menopause and extracted their outcomes. This list was refined and entered into a two-round modified Delphi survey, which was open to clinicians, researchers, and postmenopausal women from November 2019 to March 2020. Outcomes were scored on a nine-point scale from “not important” to “critically important.” The final COS was determined following two international consensus meetings.

**Results:** A total of 26 unique outcomes were included in the Delphi process, which was completed by 227 participants of whom 58% were postmenopausal women, 34% clinicians, and 8% researchers. Predefined thresholds

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were applied to the Delphi scores to categorize outcomes by importance, which informed the e consensus meetings, attended by 43 participants from 21 countries. The final COS includes eight outcomes: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort or irritation, (4) discomfort or pain when urinating, (5) change in most bothersome symptom, (6) distress, bother or interference of genitourinary symptoms, (7) satisfaction with treatment, (8) side effects of treatment.

**Conclusion:** These eight core outcomes reflect the joint priorities of postmenopausal women, clinicians, and researchers internationally. Standardized collection and reporting of these outcomes in clinical trials will facilitate the comparison of different treatments for genitourinary symptoms, advance clinical practice, and ultimately improve outcomes for symptomatic women.

**Key Words:** Clinical trials – COMMA – Core Outcome Set – COS – Genitourinary symptoms – Menopausal symptoms – Menopause – Vaginal dryness – Vulvovaginal atrophy.

**Video Summary:** <http://links.lww.com/MENO/A765>.

Genitourinary symptoms may arise following the physiological decline in circulating estrogens associated with menopause. The most common symptoms include vulvovaginal dryness, itching, dyspareunia (pain during sex), and urinary symptoms such as painful urination. These symptoms affect more than 50% of postmenopausal women and tend to persist into older age.<sup>1</sup>

Randomized trials investigating treatments for genitourinary symptoms associated with menopause have reported many different outcomes, with extensive variation in how these outcomes are defined.<sup>2</sup> For example, the severity or presence of vulvovaginal atrophy has been evaluated using measures such as histological appearance of vaginal epithelial cells, vaginal pH, a clinician assessing the appearance of the genitals, or by a woman's self-report of her symptoms. It is uncertain whether "objective" measures such as clinician report or superficial cell morphology align with the nature or severity of genitourinary symptoms as reported by symptomatic women, or the degree of bother or interference in daily life.<sup>3,4</sup> The most commonly reported outcomes in clinical trials are the appearance of vulvovaginal atrophy and sexual function.<sup>2</sup> Other common outcomes include vaginal dryness causing discomfort during sexual activity. How symptoms impact daily life and activities has also been measured, using concepts such as interference and bother.<sup>5,6</sup> Many clinical trials have, however, not included these outcome measures. This may be partly due to a focus on obtaining regulatory approvals. For example, the Food and Drug Administration (FDA) has published guidance for the assessment of estrogen-based therapies in postmenopausal women, which instructs on study eligibility criteria and recommends reporting of three specific outcome measures (vaginal pH, most bothersome symptom, and vaginal maturation index).<sup>7</sup> The reasons for selecting these three outcomes measures is, however, uncertain.

Despite the large number of published clinical trials of treatments for genitourinary symptoms associated with menopause,<sup>2</sup> the variation in outcome reporting has made it difficult to compare and combine data across different trials. This limits the ability to determine which treatments are most effective and impedes the translation of research findings into evidence-based care in menopause.

One approach to address this variability in outcome reporting is the development and implementation of a Core Outcome Set (COS). This is an agreed minimum dataset to be routinely collected in all treatment studies for a specific condition.<sup>8</sup> COS is developed with involvement from key stakeholders (e.g., clinicians, researchers and people with lived experience of the condition) to reflect the priorities of all relevant groups.<sup>8</sup> COS establishes a short list of core outcomes, with associated definitions and guidance on how to measure and report these. There is now robust and standardized guidance available for the development of COS, from the COMET (Core Outcomes Measures in Effectiveness Trials) initiative.<sup>8</sup> Menopause has been recognized as a clinical area in need of standardized, patient-focused outcomes by the Core Outcomes in Women's and Newborn Health (CROWN) initiative.<sup>9,10</sup> The COMMA: Core Outcomes in Menopause initiative was established to develop, disseminate, and implement a COS to be used in future clinical trials evaluating interventions for vasomotor symptoms and genitourinary symptoms associated with menopause.

## METHODS

The COMMA project was prospectively registered with the CROWN and COMET initiatives (registration no. 917), and the protocol has been described previously.<sup>11</sup> Briefly, a COMMA Steering Group was convened to provide oversight on the scope and progress of COMMA. The Steering Group included international representation from all three participant groups: women who self-identified as postmenopausal women, and clinicians and researchers with expertise in menopause. The Steering Group was established by identification of relevant individuals via existing networks of the COMMA project lead (M.H.), and through contacts of these. The scope of this COS was restricted to clinical trials evaluating interventions for genitourinary symptoms associated with menopause, regardless of the cause of menopause or the intervention being studied. COS for other symptoms of menopause, such as vasomotor symptoms, will be published separately.

## Systematic review and Delphi survey

We performed a systematic review of randomized controlled trials of treatments for genitourinary symptoms associated with

menopause and extracted all outcomes.<sup>2</sup> These outcomes were assembled into a long list which was reviewed by the Steering Group to combine similar outcomes (e.g., vulvar pruritus and vulvar itching were merged into one outcome) and to ensure comprehension and use of lay terminology. The list of outcomes was entered into a modified two-round Delphi survey, completed by three groups: postmenopausal women, clinicians, and researchers with expertise in menopause. The Delphi technique is a widely recognized methodology for COS development. It facilitates anonymous participation from a large group of individuals without restrictions based on geography, and reduces the influence of dominant participants.<sup>8</sup> The survey used a hover function that permitted the display of lay definitions and explanation of technical terms to further reduce ambiguity and facilitate participation from postmenopausal women. The survey was pilot-tested amongst the Steering Group, including postmenopausal women, prior to being distributed as widely as possible. The survey was sent to community and advocacy groups in menopause; international professional societies (in endocrinology, obstetrics and gynecology, menopause, and primary care); specialists in breast, gynecologic, and hematological cancers; nurses; nurse practitioners; psychologists; physiotherapists; journal editors; funding bodies; the Cochrane Collaboration; researchers; and clinicians working in menopause, and through personal contacts of the Steering Group. Recruitment efforts specifically aimed to gain representation from low- and middle-income countries to ensure responses reflected the priorities of different groups, geographically and culturally. Women from the community who self-identified as having experienced menopause were recruited. These women likely represent predominantly postmenopausal woman and we therefore use the term “postmenopausal” to refer to these participants, although women in the menopausal transition also participated.<sup>12</sup> Women likely considered their experience of both the menopause transition and postmenopause in contributing to this study. We did not verify reproductive stage using STRAW criteria.<sup>12</sup> No restrictions were placed on cause or age of menopause and participants included women experiencing spontaneous menopause at the average age, women with primary ovarian insufficiency, premature menopause (before the age of 40 years) or early menopause (before the age of 45 years), surgical menopause, radiation or chemotherapy-induced menopause, and menopausal symptoms secondary to endocrine therapy for breast cancer.

We requested all participants to complete both rounds of the Delphi survey. In each round, participants were asked to rate the importance of each outcome on a Likert scale from 1 to 9 (1 “not important”, and 9 “of critical importance”), or to indicate that they were unable to score the outcome. In Round 1, there was an option to suggest additional outcomes for consideration of inclusion in Round 2. Only participants who had completed Round 1 were invited to contribute to Round 2. In Round 2, participants were presented with the aggregate outcome scores from Round 1, organized by participant group, and were also able to compare this against how they had scored each item in

the previous round. This process encourages participants to reflect on their previous scores and consider the views of others when rescoring each item, thereby helping to achieve convergence over multiple rounds.<sup>8</sup>

Following the completion of Round 2, predefined consensus criteria were applied to classify each outcome as<sup>11</sup>:

- Consensus in: outcomes which more than 70% of participants in each group scored as “of critical importance” and fewer than 15% of participants in each group scored as “not important.”
- Consensus out: outcomes which more than 70% of participants in each group scored as “not important” and fewer than 15% of participants in each group scored as “of critical importance.”
- No consensus: outcomes not meeting either of the above criteria

To visualize the level of agreement in scores between participant groups we produced scatterplots of median scores for each of the outcomes, for the three different pairs of participant groups (clinicians vs postmenopausal women, researchers vs postmenopausal women, and researchers vs clinicians).

### Consensus meetings

A consensus meeting was planned in conjunction with the biannual International Menopause Society World Congress which was scheduled to be held in Melbourne, Australia in April 2020. This was replaced by two international videoconferencing meetings that were held in May and June 2020 due to the COVID-19 pandemic. Two meetings accommodated attendees from different time zones to enhance representation from a broader range of geographical locations including middle- and low-income countries than may have been achieved at an in-person conference. At these meetings, attendees reviewed the results of the Delphi survey, with particular reference to the allocation of each outcome as consensus in, consensus out, and no consensus. The aim of the meetings was to reach consensus about which outcomes should be included in the final COS. The meetings followed an informal approach and were moderated by an assigned Chair (S.L.). Voting was used only when consensus could not be reached by discussion. The meetings were 2 hours in duration and were attended by postmenopausal women, clinicians, and researchers with expertise in menopause. Individuals attending these meetings were identified by members of the Steering Group as either clinicians or researchers working in menopause and snowballing amongst those invited. We also included journal editors from major reproductive and menopause journals. Postmenopausal women were identified through clinical contacts of the Steering Group and networks of advocacy groups. This methodology was undertaken in parallel with the development of a COS for menopausal vasomotor symptoms, the results of which will be reported separately.

### Sample size

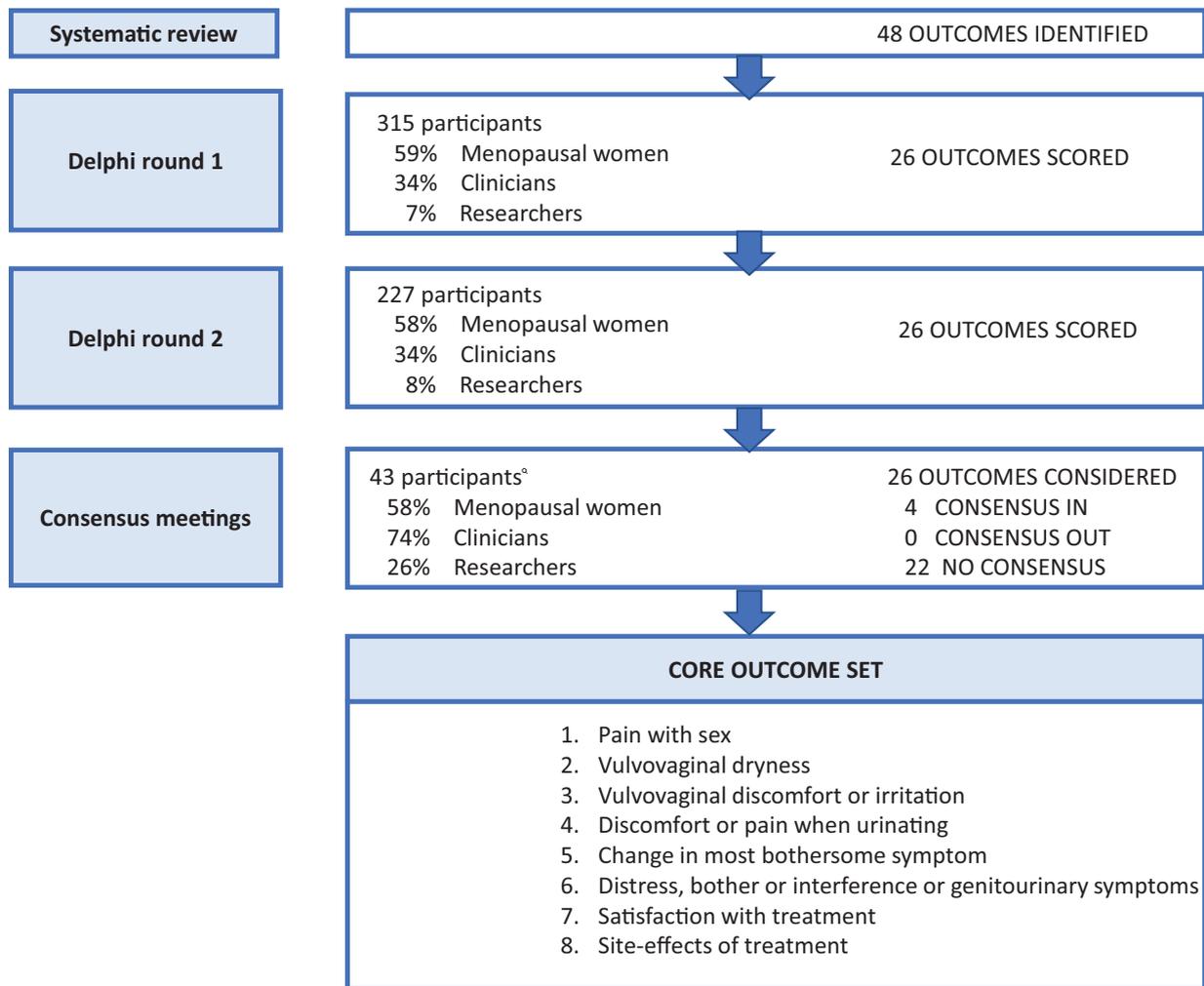
The Delphi methodology is not based on statistical power. It has previously been demonstrated that between 10 and 15 participants per group is sufficient to ensure validity,<sup>13</sup> we

aimed to recruit at least 20 participants per participant group at each Round of the Delphi survey. Ethics approval was not required as this was considered a service evaluation and development project.

**RESULTS**

The systematic review identified 48 different outcomes reported in randomized trials of interventions for menopausal genitourinary symptoms (Supplemental Table 1, <http://links.lww.com/MENO/A764>).<sup>2</sup> After review and the collapse of similar outcomes into outcome types, 26 unique outcomes were entered into Round 1 of the Delphi survey (Supplemental Table 2, <http://links.lww.com/MENO/A764>, Fig. 1). In total, 315 participants completed Round 1, which was open from 26 November to 28 December 2019 (Supplemental Table 3, <http://links.lww.com/MENO/A764>). In Round 1, participants suggested a total of 193 additional outcomes. These largely related to psychological symptoms, changes in memory and concentration, sleep disturbance and joint pains, and as a result nine additional outcome types were entered under a new domain into Round 2 (merging similar outcomes

together into outcome types, for example, irritability and mood swings were merged into mood disturbance). As this manuscript reports on the development of a COS for genitourinary symptoms, scoring data relating to these additional outcomes will be reported separately. Round 2 of the Delphi survey was open from 1 February to 15 March 2020. A total of 227 participants completed the Round 2 survey, which constituted 72% of those who had completed Round 1. Most participants self-identified primarily as postmenopausal women (58%), and in total 85% of participants were women who had experienced menopause since many of the participating clinicians and researchers were also postmenopausal women (Supplemental Table 3, <http://links.lww.com/MENO/A764>). Inspection of scatter plots suggested that importance rankings were similar between the three participant groups, indicating adequate consensus across the two Delphi rounds and therefore that a third round of the Delphi survey was not required (Supplemental Fig. 1, <http://links.lww.com/MENO/A764>).<sup>8</sup> Application of the predefined consensus criteria resulted in the categorization of four outcomes as ‘‘consensus in,’’ and the remaining 22 as ‘‘no consensus’’ (Supplemental



**FIG. 1.** Participants and outcomes contributing at each stage of the Core Outcome Set (COS) development. <sup>a</sup>For the consensus meeting, participants could elect to represent multiple participant groups.

Table 2, <http://links.lww.com/MENO/A764>). None of the outcomes met the criteria for “consensus out,” and all 26 outcomes were therefore discussed at the final consensus meetings.

Individuals from all three participant groups (postmenopausal women, clinicians, and researchers) were invited to the consensus meetings, which were attended by a total of 43 participants (Table 1). Several participants declared financial relationships with pharmaceutical companies; however, the Steering Group did not consider that these conflicts presented a threat to the integrity of the process. Of the four outcomes rated as “consensus in” during the Delphi survey, three were selected as core outcomes – two of which were merged as deemed similar (distress/bother from genitourinary symptoms and interference/bother from genitourinary symptoms) (Supplemental Table 2, <http://links.lww.com/MENO/A764>). The fourth, “severity of genitourinary symptoms” was considered to better describe a method of measuring individual genitourinary symptoms (e.g. *severity* of vaginal dryness), rather than a distinct outcome in itself, and therefore was not included. An additional five outcomes were also selected for inclusion in the COS, based on the Delphi results and extensive discussion among the attendees. The two consensus meetings yielded very similar conclusions, and these were discussed at two final Steering Group meetings in June 2020. The final COS includes eight outcomes to be reported in all future clinical trials for genitourinary symptoms: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort or

irritation, (4) discomfort or pain when urinating, (5) change in most bothersome symptom, (6) distress, bother, or interference of genitourinary symptoms, (7) satisfaction with treatment, and (8) side effects of treatment (Fig. 1).

**DISCUSSION**

This manuscript presents the results of the COMMA project, an international consensus process, which has delivered a COS for clinical trials of treatments for genitourinary symptoms associated with menopause. The COS is applicable to all trials in women with genitourinary symptoms associated with menopause, including women in the menopause transition and postmenopause. In total, eight core outcomes were selected including three measures of vaginal and/or vulvar discomfort, one measure of urinary discomfort, one measure capturing the degree of bother associated with symptoms (change in the most bothersome symptom), one measure of symptom impact (distress, bother or interference), and two general measures of patient satisfaction and treatment side effects. All except one of the core outcomes are self-reported by women. Objective measures (such as vaginal pH, superficial appearance of vagina cells, and clinician assessment of genital appearance) were included in the Delphi survey but were not considered sufficiently important by any of the participant groups and hence were not included in the COS; although there is evidence to suggest these measures correlate with symptoms.<sup>14</sup> We are aware that current FDA guidelines require the measurement of vaginal pH and vaginal maturation index as coprimary endpoints in trials of estrogen and estrogen-like therapies for genitourinary symptoms in postmenopausal women.<sup>7</sup> Following a rigorous consensus process, these outcomes were, however, not considered a priority by postmenopausal women, clinicians, or researchers in the field. Similarly, genital rather than urinary symptoms were prioritized across stakeholder groups. Urinary symptoms such as incontinence and urgency are highly prevalent in women and prospective longitudinal studies have largely failed to demonstrate that these symptoms increase in prevalence over the menopause transition or postmenopause.<sup>15,16</sup> As a result, neither urinary urgency nor recurrent urinary tract infections were selected as core outcomes. This differs from the “Genitourinary Syndrome of Menopause” which include both urinary urgency and recurrent urinary tract infections as core symptoms of menopause.<sup>17</sup>

The COMMA initiative aims to standardize the collection and reporting of research outcomes in menopause worldwide and ensuring that reported outcomes reflect the priorities of women seeking effective treatments, their clinicians and researchers in this field. Implementation of this COS will ensure that these priorities are addressed and will improve the consistency of outcome reporting in clinical research in menopause, facilitating, comparing, and combining findings from multiple clinical trials. These eight included outcomes represent a minimum dataset. The COMMA process has not endorsed any single outcome to be considered a primary outcome and did not weight the importance of these outcomes

**TABLE 1.** Participants attending the COMMA consensus meetings

Consensus meeting participants (n = 43)	n (%)
Type of participant <sup>a</sup>	
Menopausal woman	25 (58)
Natural	16 (37)
Surgical	4 (9)
Treatment related	1 (2)
Unknown	4 (9)
Gynecologist	28 (65)
Endocrinologist	9 (21)
Menopause society member/representative	19 (44)
Researcher or methodologist	11 (26)
Journal editor/representative	4 (9)
General practitioner	1 (2)
Pharmaceutical industry	0 (0)
Sex	
Female	27 (63)
Male	16 (37)
Involved in menopause research	38 (88)
Age	
31-39	1 (2)
40-49	6 (14)
50-59	19 (44)
>60	17 (40)
Geographical place of birth	
Africa	2 (5)
Asia	13 (30)
Australia/New Zealand	7 (16)
Europe	11 (26)
North America	8 (19)
South America	2 (5)

<sup>a</sup>Participants may contribute to more than one category type (e.g., an individual participant may be a gynecologist, journal editor, and a menopausal woman).

compared to each other. It is expected that researchers may also wish to include additional outcomes which are relevant to specific studies, or to specific regulatory requirements such as those issues by the FDA. The lack of importance assigned to vaginal pH and maturation index in this study may, however, challenge the draft FDA guidance for reporting of these outcomes as co-primary endpoints in trials evaluating interventions for genitourinary symptoms, and may prompt revision and finalization of this guidance to ensure it reflects outcomes of importance to patients, clinicians, and researchers.<sup>7</sup>

Although we recommend implementation of this COS in clinical trials of treatments for genitourinary symptoms, the outcomes are also likely to be relevant for other study designs, including observational studies.

The selection of outcomes took into consideration that COS are more likely to be widely implemented when the list of outcomes is short.<sup>18</sup> It is not anticipated that the selected eight outcomes will increase the burden for researchers or trial participants, as the included measures are already commonly reported in clinical trials of treatments for genitourinary symptoms.<sup>2</sup> Since the majority of outcomes are self-reported by the woman, no specialized laboratory equipment or resources are required and implementation of this COS is unlikely to incur additional costs to researchers. In addition, collection of these core outcomes will not require women participating in clinical trials to undergo additional genital examination to collect outcome data, which may dissuade women from participating in clinical trials or cause discomfort and embarrassment. We recognize that clinical examination is, however, required when clinically indicated, for symptoms such as postmenopausal bleeding or diagnosis of infections.

### Next steps and implementation

Having achieved consensus on which outcomes should be reported in clinical trials of treatments for genitourinary symptoms associated with menopause, the next step is to determine how these outcomes are best defined and measured. This process requires the systematic identification and critical appraisal of existing definitions and tools for measuring each of the core outcomes, including capture of relevant measurement properties such as content validity, structural validity, and reliability of these measures in symptomatic women. This process will follow established COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and COMET methodologies,<sup>19</sup> and result in the recommendation of the most appropriate measures. Many of the included outcomes can be measured using existing frequency or severity scales. The outcome of change in most bothersome symptom is likely to be based on individual selection of one of the four self-reported measures (pain with sex, vulvovaginal dryness, vulvovaginal discomfort or irritation, discomfort or pain when urinating) as most bothersome. Confirmation of the definition and instrument to measure change in most bothersome symptom will, however, require a comprehensive assessment of the validity and reliability of

existing instruments. The COS also includes the outcome of distress/bother/interference due to genitourinary symptoms, which aims to capture the impact or consequences of these symptoms on daily life and functioning. Satisfaction with treatment and side effects of treatment appear to be reported less often in randomized trials.<sup>2</sup> We recognize that side effects are likely to differ substantially between treatment approaches, and therefore the outcome definition will reflect this. For example, pharmacological interventions, devices, and behavioral interventions for genitourinary symptoms are likely to have different side effect profiles.

This manuscript reports a COS for use in trials of women with genitourinary symptoms associated with menopause, and the results of a parallel process to deliver a COS for vasomotor symptoms will be reported separately. We also recognize the importance of other symptoms associated with menopause such as psychological symptoms, changes in memory and concentration and joint pains, as proposed during the Delphi process and the Steering Committee will discuss how these might best be addressed in future studies.

### Strengths and limitations

The COMMA project followed robust and standardized methodology recommended by COMET, including adherence to predefined methods as published in the study protocol.<sup>8,11</sup> The development of this COS included input from a wide range of participants at all stages of the process, including the consensus meetings. We, however, did not include representatives from regulatory bodies, such as the FDA or European Medicines Agency. Participants included postmenopausal women from the community, healthcare professionals who treat symptomatic women, and researchers who conduct and publish research in this field. Input from these key participant groups helps to ensure the selected core outcomes are important to those involved in research and affected by research outcomes, including women with genitourinary symptoms of menopause. The involvement of these three groups is a strength of this COS over recommendations by other groups such as regulatory bodies. Researchers aiming for regulatory approval should be compliant with all relevant guidance, including this COMMA COS.

We maintained anonymity of all participants during the Delphi phase, which helps to avoid any influence of more powerful individuals or participant groups.<sup>20</sup> We observed a high level of agreement in scoring of the importance of all outcomes, both between participant groups and across the two consensus meetings held. The Delphi survey suffered from a 28% attrition rate between the two rounds. Although attrition introduces a risk of bias, some attrition is generally unavoidable and the retention rate is comparable to, or higher than, other similar COS Delphi processes.<sup>21,22</sup> Although focus groups are often held during COS development to increase certainty that all relevant outcomes have been considered, we did not employ this methodology. We ensured that there was, however, substantial representation of postmenopausal women at all stages of the COS development. The list of

outcomes entered into the Delphi process was developed through a systematic review of clinical trials, and we acknowledge that outcome reporting in clinical trials is influenced by outcomes mandated in relevant regulatory guidelines. The list of outcomes was deemed comprehensive during review and pilot-testing by the Steering Group (which included postmenopausal women) and no relevant outcomes related to genitourinary symptoms were suggested during Round 1. Despite this, we acknowledge that methodologies vary between COS projects, and the choice of methods used may influence the final results. We circulated the Delphi survey as broadly as possible, utilizing many professional and community networks. There was substantial involvement of postmenopausal women with 85% of those completing the Delphi survey and 58% of attendees at the consensus meetings describing themselves as postmenopausal women. As such we are confident that the core outcomes reflect the priorities of this target population. Furthermore, the Delphi survey and consensus meetings both had participation from a geographically diverse range of people. Although we specifically targeted participants from low- and middle-income countries, most were from high-income countries. Two virtual consensus meetings replaced the planned face-to-face meeting and appeared to increase participation of postmenopausal women and those from low- and middle-income countries as the costs and burden associated with travelling to international conferences was not a barrier to participation.

### CONCLUSION

The COMMA process has resulted in a final COS of eight outcomes to be reported in all clinical trials evaluating interventions for women with genitourinary symptoms associated with menopause. These outcomes are (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort or irritation, (4) discomfort or pain when urinating, (5) change in most bothersome symptom, (6) distress, bother or interference of genitourinary symptoms, (7) satisfaction with treatment, and (8) side-effects of treatment. This COS, and the selection of specific outcome measurement instruments for their collection and reporting which will follow, will improve the standardization of outcome reporting in future research, better enabling the comparison and combination of results from different studies, and ultimately improving the care of symptomatic women.

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