

## ORIGINAL STUDY

# Protocol for development of a core outcome set for menopausal symptoms (COMMA)

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### Abstract

**Objective:** Menopause is the natural cessation of menstruation and may be accompanied by troublesome symptoms including hot flushes and night sweats (vasomotor symptoms) and genitourinary symptoms. Randomized trials evaluating the safety and effectiveness of interventions for these symptoms have reported a wide range of outcomes and used inconsistent measures. This variation precludes comparing and combining data from different trials. To overcome this limitation, we will develop a Core Outcome Set for Menopausal Symptoms.

**Methods:** We will systematically review the literature to identify the outcomes reported in the interventional trials for vasomotor and genitourinary symptoms. This list will be entered into a two-round modified Delphi survey to be completed by clinicians, researchers, and consumers (women who have experienced menopause). Participants will score outcomes on a nine-point scale from “not important” to “critically important.” Representatives from each stakeholder group will then meet to discuss the results and finalize the Core Outcome Set. Ethics approval was not required as this was considered service evaluation and development. The study is registered with the Core Outcome Measures in Effectiveness Trials Initiative (<http://www.comet-initiative.org/studies/details/917>).

**Results:** An agreed upon set of minimum outcomes and outcome measures will facilitate combining and comparing findings from future trials of treatments for menopausal symptoms.

**Conclusions:** This Core Outcome Set will better enable women and clinicians to select effective treatments, improve the quality of trial reporting, reduce research wastage, and improve care for women with troublesome menopausal symptoms.

**Key Words:** Core outcome set – COMMA – Genitourinary symptoms – Menopausal symptoms – Vasomotor symptoms.

**Video Summary:** <http://links.lww.com/MENO/A633>.

Menopause is a biological inevitability in women and is characterized by the permanent cessation of menstruation.<sup>1</sup> The average age at menopause is approximately 51 years in high-income countries but varies by ethnicity and geography.<sup>2</sup> Around 80% of women experience symptoms at menopause, with vasomotor symptoms (hot flushes and night sweats) a leading patient priority for treatment.<sup>3</sup> In addition, around 50% of postmenopausal women

report genitourinary symptoms such as vaginal dryness, genital burning, or itching.<sup>4</sup>

Randomized trials evaluating interventions for the same menopausal symptoms tend to report different outcomes and in different ways.<sup>5,6</sup> For example, randomized trials have reported the severity, frequency and interference with daily life due to vasomotor symptoms. Further, each of these outcomes can be measured in different ways. For example, the

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## METHODS

severity of vasomotor symptoms has been measured using different scales and over variable time periods. Some studies report composite measures of both severity and frequency of vasomotor symptoms in a single score.

Comparing the safety and effectiveness of treatments for menopausal symptoms has been limited by the use of different outcome measures, inconsistency in how these outcomes are measured and reported, and uncertainty about which outcomes are most important for women. Together, these problems restrict the ability for researchers to combine, compare, and contrast the results from clinical trials, and therefore limit the ability of clinicians, researchers, and patients to interpret and implement evidence-based treatment for menopausal symptoms. One method for addressing these issues is the production and implementation of a Core Outcome Set.<sup>7</sup>

A Core Outcome Set is an agreed minimum data set selected by stakeholders to be routinely collected in all treatment studies for a specific condition. Core Outcome Sets are developed in collaboration with clinicians, researchers, and people with lived experience of the condition to reflect the priorities of all key stakeholders.<sup>7</sup> The implementation of a standardized Core Outcome Set aims to address the inconsistency in outcome collecting and reporting for a given clinical condition and, in turn, to improve the quality and relevance of future research. The Core Outcomes Measures in Effectiveness Trials (COMET) initiative provides guidelines and support for the development of Core Outcome Sets across health conditions and treatments. The translational importance of these is recognized by the Core Outcomes in Women's and Newborn Health (CROWN) initiative.<sup>8</sup>

The aim of this study was to produce, disseminate, and implement a Core Outcome Set for Menopausal Symptoms (COMMA).

**Prospective registration**

This project has been prospectively registered with the CROWN and the COMET initiatives (<http://www.comet-initiative.org/studies/details/917>).

**Steering group**

An international steering group including healthcare professionals, researchers working in menopause, and consumers (women with lived experience of menopause symptoms) was formed in 2016 to direct the development of the Core Outcome Set. The steering group will communicate regularly to ensure oversight of the conduct and progress of the COMMA project.

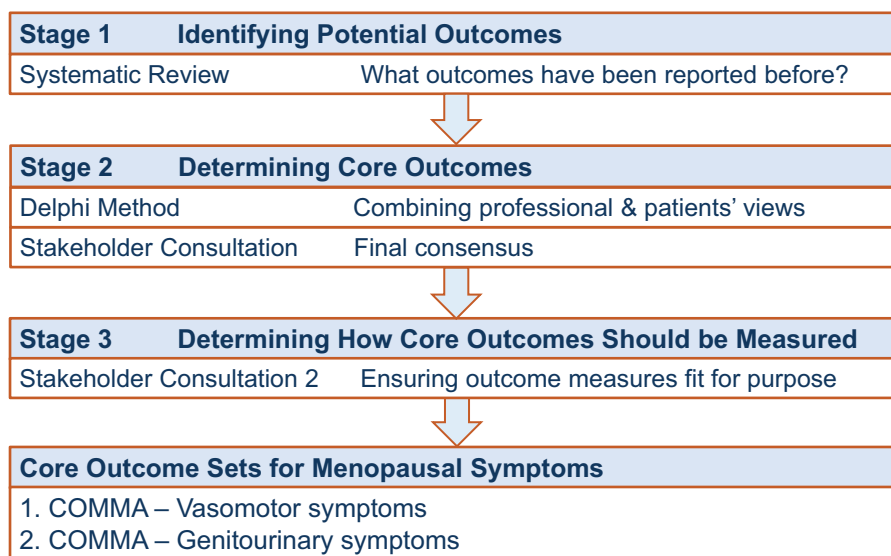
**Scope**

The steering group has recommended that COMMA develop a Core Outcome Set for vasomotor and genitourinary symptoms associated with menopause. The Core Outcome Set will be recommended for inclusion in randomized trials of interventions for these symptoms.

The methods were informed by the COMET handbook,<sup>7</sup> a systematic review of core outcome sets relevant to women's health,<sup>9</sup> and the experience of Steering group members developing core outcome sets in other areas.<sup>10-16</sup>

**Stage 1: identifying potential outcomes**

The stages of Core Outcome Set development are outlined in Figure 1. Two systematic reviews of randomized trials evaluating treatments for vasomotor and genitourinary symptoms have been undertaken.<sup>5,6</sup> Outcomes identified in each of these reviews were compiled into comprehensive lists. In consultation with the steering group (including consumer representatives), similar outcomes were merged and lay



**FIG. 1.** The core outcome set development process for COMMA (adapted from Duffy 2016<sup>12</sup>). COMMA, Core Outcome Set for Menopausal Symptoms.

definitions and appropriate terminology for the outcome names and descriptors were developed. The outcomes were then categorized into three domains: vasomotor symptoms, genitourinary symptoms reported by consumers, and genitourinary evaluations by a clinician.

### Stage 2: determining core outcomes, Delphi survey

The Core Outcome Set will be established using a modified Delphi method after recommended practices of COMET.<sup>7</sup> This process facilitates convergence between stakeholders toward consensus on the Core Outcome Set by permitting repeated reflection and rescoring of outcomes, having considered stakeholder opinions. Web-based surveys will be used as these facilitate international participation and are feasible, efficient, and acceptable to users. A two-round Delphi is planned, with an optional third round if deemed necessary by the steering group. Stakeholders will be invited to register for the COMMA survey online and asked to commit to all rounds of the Delphi process. DelphiManager survey software will be used, which is an accessible system developed specifically for Delphi surveys (Liverpool, England).<sup>17</sup> E-mail reminders will be sent in efforts to minimize attrition rates between the rounds.

### Pilot

A Pilot Delphi survey will be designed and tested within the steering group to ensure the ease of use and comprehensiveness of the outcomes included before launching the survey.

### Round 1

Key stakeholders have been identified in consultation with the steering group and include consumers, researchers working in women's health and menopause, clinicians in primary and tertiary care, advocacy groups, journal editors, and members of international menopause societies. The survey will be widely distributed in attempts to recruit individuals from differing ethnic and geographical locations.

Participants will be asked to score each outcome on a nine point Likert scale (1 to 3 = not important for inclusion, 4 to 6 = important but not critical, and 7 to 9 = critical for inclusion) after the Grading of Recommendations, Assessment, Development, and Evaluation guidelines.<sup>18</sup> To ensure comprehensiveness of outcomes, participants will be invited to suggest additional outcomes in round 1 that are not captured by those already listed. These additional outcomes will be reviewed by the steering group for consideration of inclusion in the second survey round.

### Round 2

All participants completing round 1 will be requested to complete round 2. The responses from round 1 will be summarized and presented to the participants in round 2, subgrouped by stakeholder group (consumers, researchers, and clinicians). This permits participants to review and reflect on their previous scores and the scores of others before re-

scoring each outcome. The responses from round 2 will be collated. The following consensus criteria will then be applied to classify outcomes:

- Consensus in: Outcomes that more than 70% of participants in each stakeholder group scored as "critical for inclusion" and less than 15% of participants in each stakeholder group scored as "not important for inclusion."
- Consensus out: Outcomes that more than 70% of participants in each stakeholder group scored as "not important for inclusion" and less than 15% of participants in each stakeholder group scored as "critical for inclusion."
- No consensus: outcomes not meeting either of the above criteria.

The results will be presented to the steering group for consideration for an optional third Delphi round that may be indicated if responses from different stakeholder groups are incongruent. During data analysis, anonymity of each participant will be ensured with the use of an identification code.

### Stage 3: consensus meeting

The steering group and representatives from each stakeholder group from a wide geographical and ethnic background and range of experience and expertise will meet to determine the final Core Outcome Set. This meeting was planned to be held alongside the World Menopause Conference, May 2020. Due to postponement of this event and ongoing restrictions on international travel due to the COVID-19 pandemic, consensus will now be achieved via videoconferencing. Findings from the Delphi rounds will be presented and discussed, ensuring active participation from all stakeholder groups. The meetings will determine the final core outcome set, focusing on those outcomes, which did not reach consensus in the Delphi Surveys.

### Stage 4: determining how and when core outcomes should be measured

Once the Core Outcome Set has been finalized, we will determine how and when each outcome should be measured, including appropriate measurement tools. The process of identifying, evaluating, and selecting the definitions and measurement instruments for each core outcome will follow an established COnsensus-based Standards for the selection of health Measurement INstruments and COMET process,<sup>19</sup> and methodology informed by other Core Outcome Sets in women's health.<sup>11-13</sup> This will include a systematic review of existing tools, quality appraisal of these tools for content validity, internal consistency, and feasibility of use before the final consensus decision about which tools should be recommended. The systematic review component has already been completed.<sup>5,6</sup> COMMA is actively collaborating with researchers developing measurement tools for Genitourinary Syndrome of Menopause.<sup>20</sup>

## RESULTS

COMMA will produce the first Core Outcome Set for the measurement of vasomotor symptoms and genitourinary symptoms associated with menopause. This will be a

minimum set of measures to be included in future clinical trials, considered to be most relevant to menopause by consumers, clinicians, and researchers.

A dissemination and implementation plan will be developed by the Steering group. This plan will include measures to promote awareness and facilitate implementation of the final Core Outcome Set in future trials and research studies.<sup>7</sup> In addition to publication and dissemination at relevant conferences, this plan may include direct dissemination to specialist and general journals including Cochrane, guideline producers, regulators, and international menopause societies. Additional elements may include liaising with trial and systematic review registries to embed and promote uptake of the Core Outcome Set.

## DISCUSSION

Randomized trials of interventions for menopausal symptoms report many different outcomes and assess these outcomes in many different ways.<sup>5,6</sup> This prevents researchers, clinicians and patients from combining and comparing results from different studies, limits the ability of meta-analyses to reach firm conclusions, and complicates clinical decision-making. The development of a COMMA will address this by ensuring that future trials report outcomes that are important for all stakeholders in a consistent and meaningful way. At least 337 Core Outcome Sets have been developed across numerous health domains.<sup>21</sup> Successful implementation of these measures has already reduced heterogeneity, enhanced meta-analyses, reduced the risk of reporting bias, and informed clinical and guideline recommendations and decisions across a range of health areas.<sup>22</sup>

Treatments for menopausal symptoms may only target specific symptoms, such as antidepressants for vasomotor symptoms or topical estrogen for vaginal dryness or may target multiple symptoms such as systemic hormone therapy.<sup>23,24</sup> To address this COMMA will develop two separate Core Outcome Sets for vasomotor symptoms (COMMA - vasomotor symptoms) and genitourinary symptoms (COMMA - genitourinary symptoms). In the future, additional Core Outcome Sets may be required for other symptoms associated with menopause such as sleep, mood, and sexual difficulties.<sup>25</sup>

The Core Outcome Set will be disseminated by scientific publications and presentations at relevant international meetings. This project is a registered COMET and CROWN initiative, supported by more than 80 journals who have registered their agreement to endorse implementation of Core Outcome Sets in Women's Health.<sup>8</sup> Future publications in these journals will be encouraged to report outcomes included in COMMA.

## CONCLUSIONS

COMMA will generate new information about the outcome priorities of consumers, clinicians, and researchers for

future clinical trials in menopause. Widespread implementation of these Core Outcome Sets will enhance the relevance and value of future clinical trials for vasomotor and genitourinary symptoms, translating into better health outcomes for women.

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