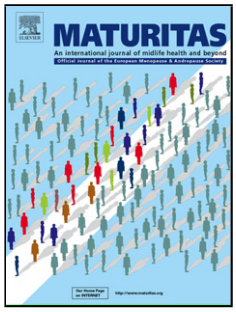

Title: Qualitative cross-cultural exploration of vaginal bleeding/spotting symptoms and impacts associated with hormone therapy in post-menopausal women to inform the development of new patient-reported measurement tools

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Qualitative cross-cultural exploration of vaginal bleeding/spotting symptoms and impacts associated with hormone therapy in post-menopausal women to inform the development of new patient-reported measurement tools

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Abbreviations:

PM	Postmenopausal
EPT	Estrogen plus Progestin Therapies
PMBQ	Post-Menopausal Bleeding Questionnaire
VBS-DD	Vaginal Bleeding/Spotting Daily Diary
PMBIQ	Post-Menopausal Bleeding Impact Questionnaire
VMS	Vasomotor symptoms
VVA	vaginal atrophy
IGM	Item Generation Meeting
VBS-DD	Vaginal Bleeding/Spotting Daily Diary
PMBIQ	Postmenopausal Bleeding Impact Questionnaire
IRB	Independent Review Board
HRQL	Health-related quality of life

ABSTRACT

Objectives

To understand the vaginal bleeding/spotting experiences of postmenopausal (PM) women taking Estrogen plus Progestin Therapies (EPT) and develop measures to assess these symptoms and their impact on women's daily lives in four countries.

Design

(1) Concept elicitation interviews were conducted with PM women in the US (n=14), Italy (n=15), Mexico (n=15) and China (n=15) to explore vaginal bleeding/spotting symptoms associated with EPT. The Post-Menopausal Bleeding Questionnaire (PMBQ) was also debriefed to evaluate understanding and comprehensiveness. (2) Based on concept elicitation, a single item electronic daily diary was developed and the PMBQ modified to form a 12-item impact measure. (3) The measures were pilot-tested and then cognitively debriefed with US women receiving EPT. All qualitative data was subject to thematic analysis.

Main outcome measures

The Vaginal Bleeding/Spotting Daily Diary, (VBS-DD) and Post-Menopausal Bleeding Impact Questionnaire (PMBIQ) were developed in this study.

Results

Concept elicitation identified vaginal bleeding and spotting as important symptoms for women taking EPT, impacting their emotional wellbeing, social life, ability to move freely, clothing and sexual activity. Based on pilot testing and cognitive debriefing, women demonstrated good understanding of the VBS-DD and the PMBQ was reduced to 10 items due to conceptual redundancy.

Conclusions

Women taking EPT in US, China, Mexico and Italy reported vaginal bleeding/spotting symptoms that have a detrimental impact on their quality of life. Two new measures were developed to assess the severity and impact of vaginal bleeding/spotting specific to EPT. This work highlights the need for EPT-related symptoms to be a part of treatment decision-making.

Keywords: Qualitative research; post-menopausal; cross-cultural; vaginal bleeding; patient-reported outcomes; questionnaire development

1 INTRODUCTION

It is estimated there are over 166 million postmenopausal women in the US, Japan and the European Union (EU) (1). Due to decreasing levels of estrogens at menopause, women often experience bothersome vasomotor symptoms (VMS), vulvar and vaginal atrophy (VVA), and an increased risk of osteoporosis (2). There appear to be cultural differences in the manner and degree to which menopausal symptoms are reported (3). Hot flushes are recognized as a symptom directly associated with menopause within the Western biomedical health framework. However in other cultures, such as Japan, while thermoregulation problems are reported, these tend to be experienced as chills and shivers (4).

Estrogen plus progestin therapies (EPT) represent the current standard of care for the treatment of menopause symptoms in postmenopausal women with a uterus. While estrogens have shown success for treating climacteric symptoms, the presence of progestin is necessary to prevent endometrial proliferation (5). However, progestins in EPT are associated with side effects such as breast pain/tenderness and vaginal spotting/bleeding (6). Irregular bleeding and spotting is reported to occur in approximately 50% of women receiving continuous EPT (7). These side effects can result in women permanently discontinuing EPT, have been associated with impairments in quality of life (8) and increased healthcare resource utilization (an estimated 32,000-42,000 postmenopausal women in the US were investigated for abnormal bleeding associated with EPT in 2010 (9)).

Clinical trials aimed at evaluating the clinical benefit of novel therapies relative to existing therapies require reliable and culturally valid measures that assess not only the efficacy of the treatment (in terms of reduction in symptoms), but also benefits in terms of tolerability. A literature review identified no suitable symptom measures, but the Postmenopausal Bleeding Questionnaire (PMBQ) was identified via personal communication as a potentially appropriate impact measure. However, while the PMBQ was well-developed based upon patient focus groups, further content validity testing was deemed necessary to establish the appropriateness of the measure for these particular patient populations, which seemingly has not occurred since there is no reference to the measure in the public domain, currently. This paper thus describes qualitative research to explore patients' experiences of vaginal bleeding/spotting associated with EPT to inform the development of a symptom measure of vaginal bleeding/spotting and to evaluate the content validity of a vaginal bleeding/spotting impact measure.

2 METHODS

2.1 Overview of study

This paper reports the qualitative research findings from a three stage study (Figure 1). Although the study explored the experiences and impacts of two common EPT side effects, namely vaginal bleeding/ spotting and breast sensations, this paper focuses on the findings for vaginal bleeding and spotting only.

In Stage 1, concept elicitation interviews with women from culturally diverse backgrounds were used to understand how postmenopausal women describe the symptoms of bleeding and spotting associated with EPT and their related impacts. During this stage, an existing measure, the Postmenopausal Bleeding Questionnaire (PMBQ) was also cognitively debriefed with participants to assess its content validity as a measure of symptoms and impacts of vaginal bleeding.

Stage 2 consisted of an Item Generation Meeting (IGM) where, using findings from Stage 1, a vaginal bleeding/spotting symptom assessment (Vaginal Bleeding/Spotting Daily Diary – VBS-DD) appropriate for inclusion in clinical trials as a measure of treatment benefit for new menopausal therapies was developed. Input was sought from measurement experts, clinical experts and linguists so that item content could be developed simultaneously in the four languages (Italian, Mexican, Chinese, US-English) using natural language which was easily translatable and conceptually equivalent in each language. In addition, modifications to the PMBQ were also made based on the initial cognitive debriefing in Stage 1, once permission had been granted by the original developer of the instrument. Both the symptom assessment and the modified PMBQ (now referred to as the Postmenopausal Bleeding Impact Questionnaire [PMBIQ]) were then subjected to full cognitive debriefing in Stage 3 in the US only.

FIGURE 1 HERE

2.2 Patient Recruitment

In Stage 1, interviews were conducted with postmenopausal women receiving EPT in the US (n=14), Italy (n=15), Mexico (n=15) and China (n=15). Sample sizes were devised in consideration of what would be required to achieve conceptual saturation(10). In Stage 3, participants were all recruited from two locations in the US. Eligible postmenopausal women had to have an intact uterus and were taking EPT with at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL prior to EPT. Participants were required to have experienced an episode of vaginal bleeding or spotting on at least 2 days during the preceding 4 weeks.

2.3 Interview Procedures

The interviews were conducted by trained qualitative interviewers using a semi-structured interview guide (Appendix A). In Stage 1, the interview guide questions started open-ended to capture spontaneous mentions of concepts related to women's experiences of vaginal bleeding/spotting as a result of EPT. Following this exploratory questioning, the PMBQ was subjected to cognitive debriefing using a 'think aloud' (11) exercise. This involved the patient being asked to speak aloud her thoughts as she read each instruction and completed each item, followed by detailed questions about definitions/meanings, understanding/clarity and relevance.

In Stage 3, US-English participants attended two visits: at Visit One, the PMBIQ was debriefed using a 'think-aloud' approach. The women were then trained to complete the VBS-DD on a hand-held

electronic device (eDiary) and took it home to complete as part of a pilot testing for 12-14 days. At Visit Two the women were cognitively debriefed on the VBS-DD and their experience of completing the eDiary.

2.4 Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by an Independent Review Board (IRB) in the US for Stages 1 and 2. In Stage 1, ethical approval was also obtained in Italy and Mexico; ethical approval for a study of this nature was not required in China. Written informed consent was obtained from all participants prior to data collection.

2.5 Analysis

In both interview stages, a qualitative analysis software package (Atlas.Ti) was used to facilitate a thematic analysis of verbatim interview transcripts (12). Non-English transcripts were translated and all analyses were performed in English. In Stage 1, methods of content thematic analysis were used where verbatim quotes were assigned codes reflective of underlying concepts and conceptual saturation was evaluated (13). Saturation can be defined as the point at which no new concept-relevant information emerges from analysis of further interviews (14). In Stage 3 the cognitive debriefing transcripts were analyzed to evaluate the comprehension, interpretation and relevance of items, the appropriateness of the response options and the recall period of the PMBIQ and VBS-DD, and the ease of use of the eDiary in the women's daily routine.

3 RESULTS

3.1 Demographic and Clinical Characteristics (Stage 1 and Stage 3)

A diverse sample of postmenopausal women on EPT was recruited for both interview stages (Table 1). In total, 59 women participated in Stage 1 (n=14 in the US, 15 in Italy, n=15 in Mexico and n=15 in China,) and 20 in Stage 3 (US only). Mean age was 50 years (range 40-63) in Stage 1 and 53.4 years (range 42-61) in Stage 3. In both Stages 1 and 3, the US sample included good representation of non-Caucasian ethnicities. In China and Italy it is considered culturally inappropriate to ask about ethnicity, hence these data were not collected. Education levels ranged from high school diploma (34%, n=20 in Stage 1) to graduate or professional degree (7%, n=4).

TABLE 1 HERE

During screening women were asked to report the severity and frequency of menopausal symptoms and hormone therapy side effects experienced in the preceding 4 weeks – results are presented in Table 2. Patterns of results were generally similar across country subgroups. Of note, no women in Stage 3 reported moderate to very heavy bleeding/spotting. A higher proportion of women had been taking HT for more than a year in Stage 3 (75%, n=15) compared to stage 1 (31%, n=18).

TABLE 2 HERE

3.2 Results of Stage 1: Postmenopausal women's experience of vaginal bleeding and/or spotting symptoms

During initial open-ended questioning, 52 women (88%) reported vaginal bleeding or spotting which they attributed to taking EPT; this included 28 women (47%) who reported experiencing vaginal bleeding and 50 women (85%) who reported vaginal spotting. Table 3 provides a summary of how the women described these symptoms, with quotes grouped by concept and counts provided by country subgroup. Women described bleeding/spotting in terms of frequency, volume of blood and associated pain levels (n=16). Bleeding and spotting symptoms were described separately but the descriptions strongly suggest that they are related and on a severity continuum: i.e. spotting is a mild form of bleeding. Severity of vaginal bleeding and spotting was largely described in terms of the 'heaviness' of the flow with spotting being described as "less heavy" than bleeding. Of note, the volume of bleeding was mentioned by the majority of Italian (n=14) and Chinese (n=14) women, but not by any US or Mexican women.

The use of sanitary protection was also discussed when describing the severity of bleeding (n=6), and as a means of protecting against vaginal bleeding and spotting (n=14). Pads were most frequently reported by women when experiencing vaginal bleeding (n=8) whereas panty liners (n=10) were more likely to be used for vaginal spotting. Spotting was reported to last only 1-2 days per month by most women who discussed duration (n=9), while bleeding was reported to last longer at up to 4 days by most women (n=14). A total of 62% (n=32) of those who reported bleeding/spotting described experiencing associated pain and discomfort in various parts of the body. Eleven of these women described experiencing abdominal sensations, such as "cramping" associated with their bleeding and ten described breast sensations, including "tenderness", "swelling" and "pain".

Conceptual saturation of the vaginal bleeding/spotting concepts was achieved in the overall sample. All sub-concepts which arose in the US interviews were also reported by women in Italy, Mexico and China and no new concepts were reported. Based on the analysis of Stage 1 data, it was concluded that vaginal bleeding and spotting experienced by postmenopausal women are closely related and that spotting can be conceptualized as a milder form of vaginal bleeding.

TABLE 3 HERE

3.3 Results of Stage 1: Vaginal bleeding/spotting impacts experienced by postmenopausal women on EPT

The participants also discussed wide-ranging impacts of bleeding/spotting on their health-related quality of life (HRQL). Of those who reported vaginal bleeding/spotting, 67% (n=35) described impacts on daily activities ranging from sexual activities to chores and lifting (Table 4). Impact on sexual activities was most frequently reported (n=23), with five of those women also avoiding sex due to bleeding causing concern about possible health implications. Four women discussed embarrassment and concerns about "mess" and feeling "dirty" being a barrier to sex. Women also described having reduced sex drive and a concern that sex could make spotting worse.

Tasks requiring physical activity such as exercise (n=7), swimming (n=6) and domestic chores (n=5) were reported to be impacted by vaginal bleeding/spotting. Eight women simply stated that they were unable to exercise, while two others said they could only perform less extraneous activities and one woman reported lacking energy. Two women reported avoiding swimming due to the need for sanitary wear. Five women talked about how doing chores was more difficult or impossible due to bleeding/spotting.

Six women described being unable to wear certain types of clothing due to their vaginal bleeding/spotting. Two women discussed concern regarding their underwear being stained, while the remaining three women discussed how they were worried about getting blood on their clothes, with two women stating they avoided light colored pants because of the risk of bloodstains.

TABLE 4 HERE

For five women, their vaginal bleeding/spotting was so severe they were unable to socialize. For example, one patient avoided social engagements due to anxiety about her bleeding. Twenty of the 52 women who reported vaginal bleeding/spotting (38%) described how the symptom impacted their psychological/emotional well-being (Table 5). Worry/anxiety was the most commonly reported psychological impact (n=11): four women reported worrying about the significance or cause of their spotting and three mentioned that their vaginal spotting made them worry they had cancer. Four of these women described being so anxious about their vaginal spotting that they had sought reassurance from their physician, two of whom underwent further assessment through a gynecological examination and an ultrasound test. Worrying about bleeding in public was discussed by two women, one of whom described being so anxious about her bleeding that she often felt "rapid heartbeats".

Six women described their bleeding/spotting as an "annoyance" due to the inconvenience caused by having to go to the bathroom to change their sanitary wear or not being able to exercise. Feelings of embarrassment (n=5) and depression (n=4) were also reported. In contrast, three women reported a positive impact of this symptom, with one patient stating it gave her a sense of "peacefulness".

TABLE 5 HERE

3.4 Results of Stage 1: Debriefing of the PMBQ

Participants' feedback during the cognitive debriefing of the PMBQ indicated that all concepts measured by the PMBQ were relevant to their experience of the impact of vaginal bleeding/spotting. However it was noted that some PMBQ items assessed very broad concepts that led to inconsistent interpretation (e.g. the concept of 'mood' was assessed in the PMBQ, while specific sub-concepts of mood such as worry/anxiety, annoyance, embarrassment and depression were reported by women in this study).

Results of Stage 2: Development of Vaginal Bleeding/Spotting Daily Diary (VBS-DD) and PMBIQ

A review of the findings in the IGM suggested that most women understood bleeding and spotting to be the same symptom but that vaginal spotting is a less severe form of bleeding. Severity was considered an important quality, but it was acknowledged that making granular differentiation between the different levels of bleeding severity (i.e. light bleeding, moderate bleeding, heavy bleeding) would be difficult for participants. Frequency of vaginal bleeding/spotting was commonly discussed by women in all four countries using consistent terminology despite language differences. Given that the intended

primary endpoint in the clinical trials for which the instrument would be included was cumulative amenorrhea, it was felt the most important aspect to capture was presence/absence of bleeding on a daily basis by employing a 24-hour recall due to the daily variation of the symptom. Additionally to minimize burden on women and to ensure accurate time stamping of data collected, an electronic diary (eDiary) was selected as the mode of administration. Therefore a single-item symptom assessment was developed which asked participants to report the presence of any bleeding/spotting in the last 24 hours (VBS-DD - Vaginal Bleeding Symptom-Daily Diary). To capture gradation of severity without asking women to rate heaviness of bleeding on too granular a level, women responding 'yes' are given the choice of selecting 'spotting' or 'bleeding'. Definitions of vaginal spotting and bleeding were also developed for inclusion in this item based on Stage 1 findings: 'Spotting = no sanitary protection required except for panty liners' and 'Bleeding = sanitary protection required'.

To assess the impact of vaginal bleeding/spotting on HRQL, items in the PMBQ were modified based on Stage 1 findings and expert input, forming the 12-item Post-Menopausal Bleeding Impact Questionnaire (PMBIQ). The symptom items were removed as they are captured in the VBS-DD. Items assessing broad or ill-defined concepts (e.g. impact on 'mood') were replaced with more specific items to reduce variation in interpretation (e.g. 'make you feel annoyed' or 'make you feel anxious'). The resulting PMBIQ retained the original 4-week recall period as this was deemed acceptable by women in Stage 1 in the context of vaginal bleeding/spotting symptoms, which may only occur for a few days during a month. The resulting PMBIQ consists of 12 items assessing emotional wellbeing (6 items), social functioning (1 item), type of clothing (1 item), physical functioning (1 item) and sexual functioning (3 items).

3.5 Results of Stage 3: Pilot testing and cognitive debriefing of Vaginal Bleeding/Spotting Daily Diary (VBS-DD)

Prior to cognitive debriefing, all 20 participants completed the VBS-DD on a hand-held device for 12-14 days as a pilot test with a high completion rate (only 11% missing data). All 20 participants demonstrated excellent understanding of the VBS-DD through the 'think aloud' interview and interpreted it appropriately. The majority of participants (80%, n=16) reported the VBS-DD was relevant to their experience of vaginal bleeding/spotting, although 90% (n=18) of patients did not actually experience bleeding or spotting during the pilot test. No changes to the item content were considered necessary based on the cognitive debriefing results. Participants reported no significant issues completing the VBS-DD as part of their daily routine and 16 women (80%) were comfortable with completing the eDiary for a longer period of time. Improvements were suggested to enhance usability including accessing the eDiary from a cell phone or computer. Figure 2 presents the final conceptual framework for the VBS-DD.

FIGURE 2 HERE

3.6 Results of Stage 3: Cognitive debriefing of Post-Menopausal Bleeding Impact Questionnaire (PMBIQ)

Cognitive debriefing of the PMBIQ was conducted with four women who had experienced vaginal bleeding/spotting in the past 4 weeks and had rated it as their most severe symptom during screening. Although the sample was small it was important to include women who had real-life experience of bleeding to ensure that feedback on relevance of concepts could be obtained. Of the four women, for each PMBIQ item at least three commented that it was easy to understand. The exception was item 8 ('limit your ability to move freely') which was only understood by two women. To enhance understanding, this item was re-worded to 'limit you in moving freely'.

All concepts measured were relevant to at least one of the four women except for 'sad', 'depressed', 'limit ability to move freely', and 'limit you in doing things with family and friends'. Conceptual overlap was identified for some items (e.g. 'limit you doing things with family and friends' vs. 'social and leisure activities') resulting in the deletion of two items. The response scales were well-understood and interpreted consistently. The cognitive debriefing findings resulted in a ten-item PMBIQ; the conceptual framework is presented in Figure 3.

4 DISCUSSION

The results of initial exploratory interviews in four countries provide evidence that bleeding/spotting is a commonly experienced side effect of EPT, reported and described in a consistent manner by women in a range of different cultures, as supported in the literature (8, 15). Moreover, the results indicate that vaginal bleeding/spotting impact on postmenopausal women's HRQL including emotional wellbeing, choice of clothing, physical functioning, social functioning and sexual functioning. The specific domains of HRQL impacted varied across the sample such that the number of women affected for a specific domain was often low, but overall the impact for any one woman was often considerable. The findings supported development and refinement of two PRO measures of these symptom and impact concepts.

FIGURE 3 HERE

A strength of this research was the fact that interviews were performed in four different continents. The findings confirm that, while there were differences in how the women expressed themselves, in all four countries women reported similar symptom and impact experiences, providing evidence of cross-cultural validity. Furthermore, the simultaneous development of four language versions of the instruments ensured that the concepts measured in the VBS-DD and PMBIQ are relevant across cultures, and that the items are worded in a manner that facilitates translation, among these languages, but also into other languages in the future. Similarly, the involvement of clinical experts experienced in treating post-menopausal women was critical for ensuring the items captured all important concepts in an appropriate manner. The inclusion of women with a range of literacy and education levels in Stages 1 and 3 helped to ensure that the PROs will be comprehensible to women of all abilities. This work follows best research practice for the development and validation of PROs, as outlined in the FDA PRO guidance for industry (16) and EMA guidance on the use of health-related quality of life measures in the evaluation of medicinal products (17).

This study has highlighted the need for the burden and impact of vaginal bleeding/spotting to be considered when making treatment decisions for postmenopausal women experiencing vasomotor symptoms (18, 19). Notably, worry/anxiety was the most commonly reported psychological impact with four women reporting worry about the significance or cause of their spotting, three of whom mentioned that their vaginal spotting made them worry they had cancer. An attribution item in a measure to capture this form of cognition and its potential relationship to emotional impacts would be interesting. However as the PMBIQ is a measure of clearly defined impacts resulting from vaginal bleeding/spotting associated with EPT, such an item was not deemed suitable for inclusion. Such burdensome side effects (and their substantial impacts) can negatively impact treatment satisfaction, and therefore adherence and persistence (20). Three women in Stage 1 (China=2/9, Mexico =1/5) explicitly stated they sometimes stopped taking their HT due to bleeding side effects becoming too severe. Overall, this study highlights a need for treatments that reduce menopausal symptoms but with few side effects which impact on the patient's quality of life.

While the PMBIQ was not specifically developed to address changes in treatments per se, the results from this instrument could be used to inform clinicians as to the bothersomeness of bleeding or spotting for a given patient with the outcome determining whether a change in therapy was indicated or not. A logit, thereby, could be developed in the future to ascertain at what score(s) a therapeutic change would be justified. As such, some combination of symptom frequency/bothersomeness could be 'scaled' to measure the impact of uterine bleeding in much the same way that other symptom driven abnormalities are assessed (i.e. urinary incontinence, sexual dysfunction, etc.).

A limitation of this study is that only US-English versions of the instruments were cognitively debriefed and no further content validation work was conducted for the Italian, Mexican and Chinese measures. While the diverse range of ethnicities included in the US cognitive debriefing sample supports the generalizability of the findings, further content validity testing of other language versions is ideally recommended. Furthermore, due to time limitations, the PMBIQ was only debriefed in a very small sample (n=4), all of whom reported light to very light bleeding. Further cognitive debriefing in a larger sample of women who report heavier bleeding and will therefore experience symptoms during debriefing of the measure, is recommended to ensure all items are truly relevant and consistently understood. The next step is then to evaluate the psychometric properties of the instruments using data from a larger study, to ensure they provide endpoints that are valid, reliable and responsive to changes over time.

5 Conclusions

This work highlights that vaginal bleeding is a significant and impactful side effect of EPT, which is relevant across cultures and affects women's HRQL. The qualitative research supported the development and refinement of two PRO instruments which were shown to have strong content validity in a sample of postmenopausal women.

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Linguists/Interviewers:

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- Daniela Carboni, Consultant Psychologist, Italian Interviewer
- Gaudalupe Riego, Mexican Interviewer
- Felicitas Colombo, Director of Datos and Estragias, Mexican Interviewer

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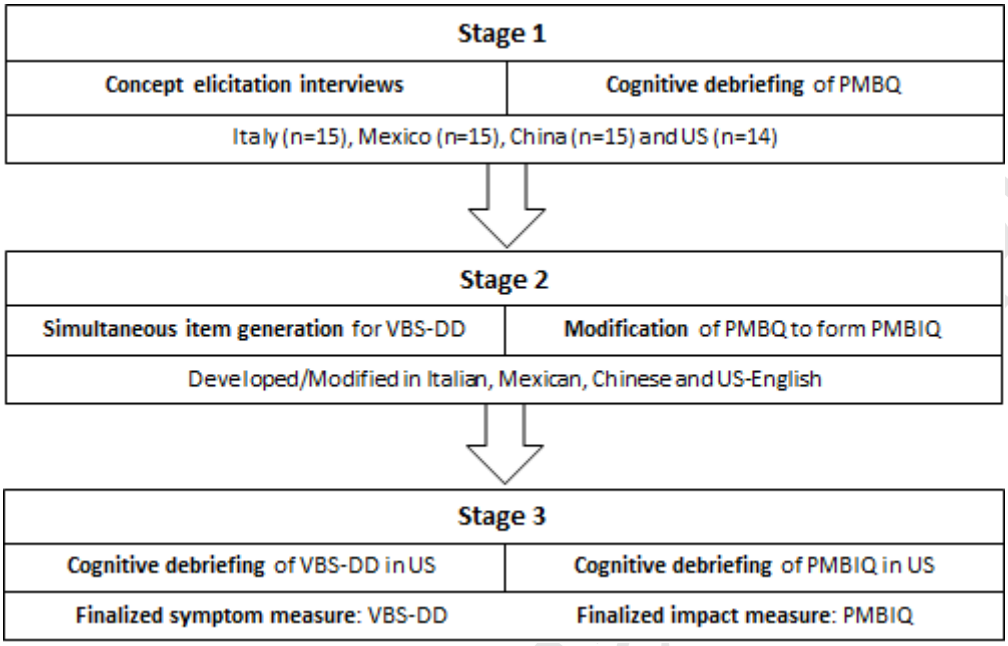
Figure 1: Overview of study



*Note: VBS-DD: Vaginal Bleeding Spotting Daily Diary, PMBQ: Post-Menopausal Bleeding Questionnaire, PMBIQ: Post-Menopausal Bleeding Impact Questionnaire

Figure 2. Final conceptual framework for VBS-DD

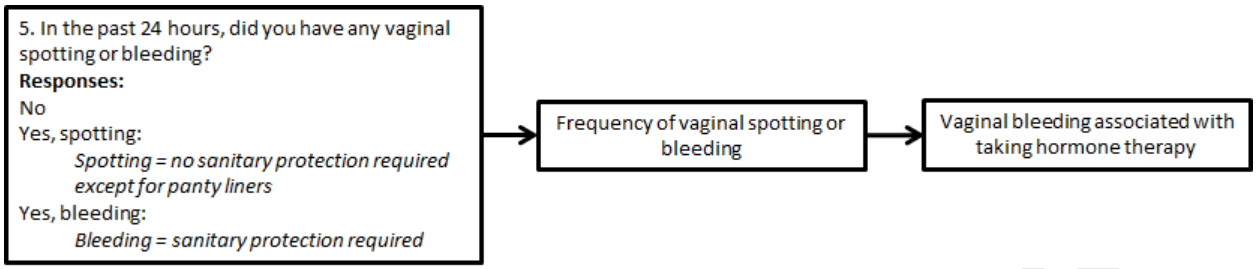


Figure 3: Final conceptual framework for the PMBIQ

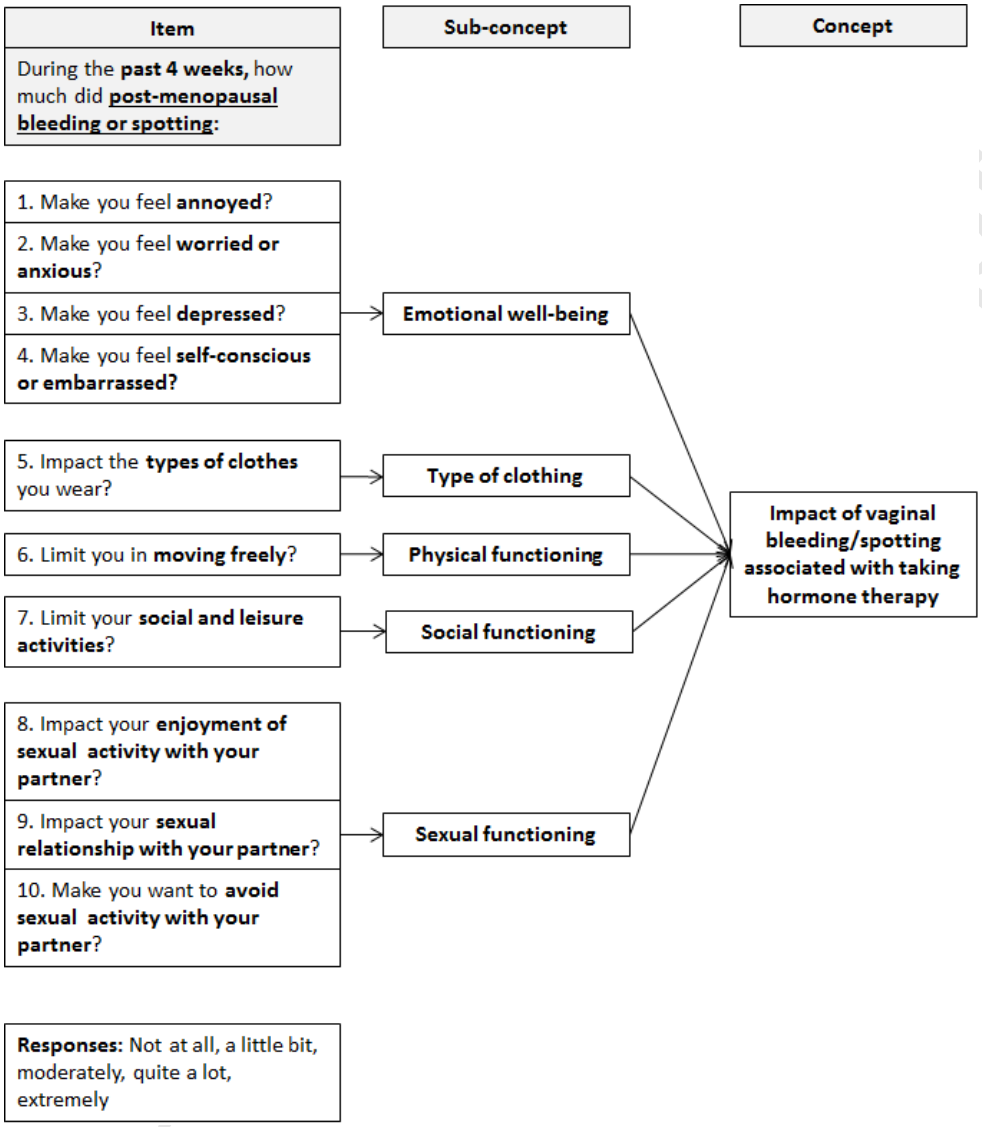


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Table 1. Demographic characteristics of sample

Demographic characteristic	% (N) of participants					
	Stage 1					Stage 3
	US (N=14)	Italy (N=15)	Mexico (N=15)	China (N=15)	Total (N=59)	US (N=20)
Mean age (min, max)	52 (41,61)	46 (40,54)	52 (47,63)	51 (41,58)	50 (40,63)	53.4 (42,61)
Ethnicity % (n)					(N=29)	
Black/African American	14 (2)	N/A	0	N/A	7 (2)	35 (7)
Hispanic/Spanish	36 (5)		80 (12)		59 (17)	5 (1)
Caucasian/White	50 (7)		20 (3)		34 (10)	55 (11)
Asian	0		0		0	5 (1)
Highest education level % (n)						
High school diploma or GED	36 (5)	40 (6)	20 (3)	40 (6)	34 (20)	15 (3)
Some years of college	28 (4)	0	13 (2)	0	10 (6)	30 (6)
Junior College degree	0	0	0	53 (8)	14 (8)	0
Certificate program	0	7 (1)	20 (3)	0	7 (4)	0
College or university degree (2 or 4 year)	36 (5)	27 (4)	33 (5)	7 (1)	25 (15)	45 (9)
Graduate or professional degree	0	20 (3)	7 (1)	0	7 (4)	10 (2)
Secretarial skills education	0	0	7 (1)	0	2 (1)	0
Junior High	0	7 (1)	0	0	2 (1)	0

Table 2: Patient-reported clinical characteristics

	% (N) of participants					
	Stage 1					Stage 3
	US (N=14)	Italy (N=15)	Mexico (N=15)	China (N=15)	Total (N=59)	US (N=20)
Severity of bleeding/spotting on average during past 4 weeks % (n)	**(N=14)**	**(N=13*)**	**(N=12*)**	**(N=13*)**	**(N=52*)**	**(N=9*)**
Very light	21 (3)	15 (2)	33 (4)	8 (1)	19 (10)	44 (4)
Light	29 (4)	38 (5)	33 (4)	46 (6)	37 (19)	56 (5)
Moderate	29 (4)	38 (5)	17 (2)	31 (4)	29 (15)	0
Heavy	21 (3)	0	17 (2)	15 (2)	13 (7)	0
Very heavy	0	8 (1)	0	0	2 (1)	0
# of days with vaginal bleeding/ spotting during past 4 weeks % (n)						
0 days	0	13 (2)	20 (3)	13 (2)	12 (7)	55 (11)
1-5 days	57 (8)	60 (9)	60 (9)	73 (11)	63 (37)	40 (8)
6-10 days	36 (5)	20 (3)	13 (2)	13 (2)	20 (12)	5 (1)
11-20 days	7 (1)	0	7 (1)	0	3 (2)	0
21-30 days	0	7 (1)	0	0	2 (1)	0
Time on current HT treatment for menopausal symptoms						
Less than 1 month	7 (1)	0	0	0	1 (1)	0
1 - 6 months	21 (3)	27 (4)	20 (3)	53 (8)	31 (18)	15 (3)
6 -12 months	43 (6)	40 (6)	40 (6)	27 (4)	37 (22)	10 (2)
More than 1 year	29 (4)	33 (5)	40 (6)	20 (3)	31 (18)	75 (15)

*Note: Only participants who reported more than 0 days of bleeding could report on the severity of their bleeding, therefore the sample size was reduced for this question.

Table 3: Patient counts and example quotes for descriptions of vaginal bleeding and spotting

Severity quality	Country				Total (n=59)	Example quotes
	US (n = 14)	Italy (n = 15)	Mexico (n = 15)	China (n = 15)		
Vaginal bleeding						
Consistency	3	1	1	0	5	It sort of has lumps. Yes, it's lumpy…well, look like pieces of liver – US, aged 61
Color	5	3	0	7	15	Sometimes it was bright red blood and sometimes it was the blood that looks a little bit darker, like it's older blood – US, aged 50
Heaviness	3	2	5	0	10	Two to three days it would be moderate, then it would come back kind of heavy, but not as heavy as it was when it first started – US, aged 61
Volume of bleeding	0	14	0	14	28	I just have to use sanitary napkins for that, but never did I have a severe bleeding. The amount was always very small, always – China, aged 44
Level of sanitary protection	2	0	0	4	6	Sometimes I'll try to get away with a pad when it's lighter, but if it's heavier then I definitely use a tampon – US, aged 50
Ease of blood flow	3	0	1	1	5	It don't come out like a normal period where you would halfway soak a pad or if you're using a tampon or whatever. It comes out and then that's it. It does it like you're spitting it out or something – US, aged 41
Duration of bleeding	1	0	0	1	2	I think about two months ago it [severe bleeding] really went on for probably, definitely pushing toward the five days and it was definitely heavier than it normally – China, aged 48
Vaginal spotting						
Color	4	7	4	3	18	Sometimes it was coffee-colored, sometimes it was bright red – China aged 48
Heaviness	2	1	5	2	10	For example, similar to sometimes when my period was finished, suddenly, after a few days, uhm, a light bleeding would occur – Mexico, aged 52
Volume of blood	3	0	3	5	11	A really tiny mild thing; a little nothing – Italy, aged 43
Level of sanitary protection	1	1	0	2	3	Sometimes I replace it with a new one because I think it's stained, not because the amount is large, actually. One pad will suffice for a day's amount without doubt – China, aged 44

Table 4: Patient counts and example quotes for daily life impacts of bleeding and spotting

Impacts on daily life	Country				Total (n=59)	Example quotes
	US (n=14)	Italy (n=15)	Mexico (n=15)	China (n=15)		
Sex life	10	4	3	10	23	…I just don't really want to be intimate…it's just extra messy – US, aged 50
Exercise	3	0	1	3	7	I try to avoid too much strenuous exercising … because I'm self-conscious of it - it might start a heavy flow at any point in time – US, aged 61
Swimming	2	2	0	2	6	When I used to have heavy bleeding before, it was inconvenient to go around for some activities, like swimming – China, aged 57
Clothing	2	0	1	3	6	I liked to wear white pants a lot and since I take these kind of pills, and I started bleeding, well, I don't wear them because I am always afraid that they could get stained at any second – Mexico, aged 52
Domestic chores	2	0	1	2	5	Housework? I think I have to take care of myself and avoid doing too much – China, aged 57
Lifting	2	0	1	0	3	I can´t lift heavy weights – Mexico, aged 52

Table 5: Patient counts and example quotes for psychological impacts of bleeding and spotting

Psychological impacts	Country				Total (n=59)	Example quotes
	US (n = 14)	Italy (n = 15)	Mexico (n = 15)	China (n = 15)		
Worry/Anxiety	6	4	3	3	16	These thing show up, I say "oh my God… have I got the sanitary napkin or haven't I?", so you feel uncomfortable, because maybe you are at some friend's home – Italy, aged 43
Annoyance	2	3	1	0	6	I would prefer that it didn't happen, because it has an annoying effect, because I've had an abundant blood stream for a long time – Italy, aged 41
Embarrassment	3	1	1	0	5	I mean if you're bleeding…it's just so embarrassing – US, aged 41
Depression	3	0	1	0	4	…because I wouldn't want that on his body parts. So I just would feel very low – US, aged 41
Positive attitude	1	2	0	1	3	Though a trouble to me in the past, menses give me a cheering message that I won't get old – China, aged 50
Feeling pre-occupied	1	1	0	0	2	No, if I'm out, it's obvious, like every woman, when, eh…. These thing show up, I say "oh my God… have I got the sanitary napkin or haven't I?" – Italy, aged 43
Lower self-esteem	2	0	0	0	2	It makes me feel like I'm no good to my partner – US, aged 61