METHOD ARTICLE

Development of a patient reported outcome questionnaire to measure the impact of postpartum blood loss in women with moderate and severe anaemia: A study using a multi-faceted approach [version 1; peer review: 1 approved, 1 approved with reservations]

Lori Miller[1], Shahana Chaudhri[2], Danielle Beaumont[1], Aasia Kayani[2], Kiran Javid[2], Rizwana Chaudhri[2], Phil Edwards[1], Amy Brenner[1], Ian Roberts[1], Haleema Shakur-Still[1]

[1]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, WC1E 7HT, UK
[2]Rawalpindi Medical University, Rawalpindi, Pakistan

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Abstract

Background: Globally, over one-third of pregnant women are anaemic and are at increased risk of postpartum haemorrhage (PPH). Tranexamic acid (TXA) given within 3 hours of birth significantly reduces death due to bleeding in women with PPH. However, for many, treatment is too late to prevent death from PPH. The WOMAN-2 trial aims to see if giving TXA can prevent PPH and other outcomes in women with moderate and severe anaemia. Assessing the impact of postpartum blood loss on women's own perceptions of their health and well-being is an important outcome for the WOMAN-2 trial. This study aimed to develop a conceptual framework and questionnaire to measure the impact of postpartum blood loss on participant-reported outcomes (PRO) in women with moderate and severe anaemia.
Methods: A conceptual framework and PRO questionnaire were developed using a multifaceted, iterative process. Factors influencing anaemic women's postpartum experience were identified from review of the literature and through group discussion with them. *De novo* items were combined with those from an existing instrument (Multi-dimensional Fatigue Symptom Inventory, Short Form (MFSI-SF)). Content validity was tested among a group of obstetricians and anaemic postpartum women, revised and then pilot tested among 124 women with moderate and severe anaemia following vaginal birth.
Results: Women with moderate and severe anaemia who experienced PPH reported more fatigue on the MFSI-SF (p=0.001); reported feeling

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1. **Shireen Meher**, University of Liverpool, Liverpool, UK
Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
University of Birmingham, Birmingham, UK

2. **Joshua P. Vogel**, Burnet Institute, Melbourne, Australia

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more ill (p=0.004); and had greater difficulty breastfeeding (p=0.039), compared to those who did not experience PPH. Compared to women with moderate anaemia, women with severe anaemia reported experiencing worse symptoms of anaemia (p=0.001) and scored worse on the MFSI-SF (p=0.007).
Conclusions: Significant differences between the scores of women who developed PPH and those who did not and the scores between women with moderate and severe anaemia indicate that the questionnaire had satisfactory construct validity.

Keywords
participant reported outcomes, postpartum haemorrhage, anaemia, questionnaire, fatigue

Corresponding author: Haleema Shakur-Still (haleema.shakur@lshtm.ac.uk)

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Introduction

There are about 100,000 maternal deaths from postpartum haemorrhage (PPH) every year with most occurring in low and middle income countries[1–4]. Of the women who survive PPH, many suffer severe morbidity including hysterectomy which removes the possibility of having more children. The morbidity associated with PPH can also interfere with breastfeeding and bonding[5,6].

Despite efforts to prevent anaemia, many women give birth with low haemoglobin levels. Anaemia increases the risk of PPH[7]. In women with anaemia, even moderate bleeding can threaten their lives. Fatigue due to anaemia restricts a mother's ability to care for her children and impacts her well-being[8]. There is an urgent need to find an effective way to reduce postpartum bleeding in anaemic women.

The recently published WOMAN Trial of tranexamic acid (TXA) in women with PPH showed that, when given within 3 hours of birth, death due to bleeding was reduced by about 30% with no adverse effects[9,10]. However, as most PPH deaths occur soon after giving birth and women with anaemia are at increased risk, treatment is too late to prevent death in many women. Trials of the prophylactic use of TXA to prevent PPH are inconclusive[11], most have serious flaws[12] and very few collected data on maternal well-being.

The WOMAN-2 trial aims to determine the effects of TXA in women with moderate or severe anaemia who give birth vaginally[13]. Results from clinical trials of TXA in elective surgery show that TXA treatment seems to move the entire distribution of bleeding towards reduced blood loss by about one third irrespective of baseline blood loss[14]. If this is also the case in postpartum anaemic women, then trial participants have the potential to benefit whether or not they experience PPH, since even moderate or mild blood loss can have adverse health consequences in anaemic women[13]. Therefore, assessing the impact of any postpartum blood loss on a woman's own perceptions of her health and well-being is an important outcome for the WOMAN-2 trial. Including participant-reported outcomes (PRO) is emphasised as a core outcome for studies evaluating interventions for prevention of PPH[15].

There are no standard measures, however, to assess the impact of blood loss on the health and well-being of women with varying degrees of anaemia at discharge from hospital after giving birth. This study aims to (1) build a conceptual framework to assess the impact of early postpartum blood loss on relevant PRO for women who give birth with moderate and severe anaemia and (2) develop a questionnaire to measure women's perceptions of aspects of their health and well-being that would be suitable for use in the WOMAN-2 trial.

Methods

An overview of the development process is provided in Figure 1.

Phase 1: Initial conceptual framework and questionnaire design

Step A: A review of the literature was conducted to identify relevant domains of health and well-being for postpartum anaemic women and to identify existing questionnaires. An initial conceptual framework and an outline set of questions were developed. A group consisting of new mothers from our patient and public involvement (PPI) group in the UK attended a face-to-face meeting and added to the relevant domains and provided feedback on the outline set of questions. The questionnaire was further revised based on this feedback, team discussion, additional literature review, and existing tools which measured domains identified as important.

Step B: A protocol for pilot testing the questionnaire was developed. To test the appropriateness of our questions, we enrolled

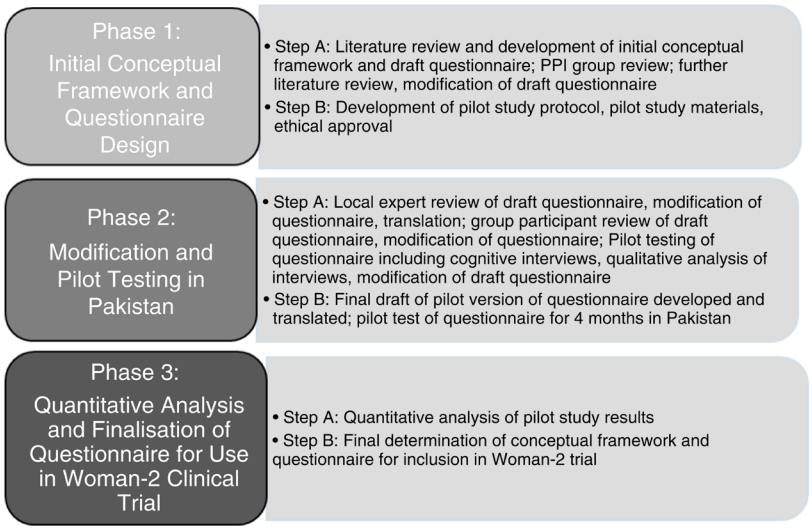

Figure 1. Conceptual framework and questionnaire development process.

anaemic women who had vaginal births with no PPH, and anaemic women who had vaginal births and experienced a PPH. Women were enrolled from the postnatal wards of one hospital in Rawalpindi, Pakistan. We hypothesized that if women who experienced a PPH or severe anaemia answered the questions differently than women who did not experience a PPH or had moderate anaemia, then the questions would be able to detect the required differences in the WOMAN-2 trial.

The pilot study objectives included: (1) assessing whether questions address outcomes and experiences relevant to anaemic women who have just given birth; (2) assessing whether questions are understood similarly by participants and research team; (3) assessing whether questions and answer choices are clearly understood by participants; (4) how to accurately translate questions and answer choices; and (5) assessing whether anaemic women with different birth experiences, such as those who suffered a PPH, answer questions differently compared to those who did not. Women were eligible for inclusion in the pilot study if they had moderate or severe anaemia (haemoglobin <10 g/dl), had given birth vaginally (up to 42 days), and had not yet been discharged from the hospital. During the study period, medical records of women who gave birth at the hospital were reviewed. Eligible women were invited to participate. The number of participants to be enrolled in this study was anticipated to be dynamic, depending on how women answered draft questions and what types of issues were identified during the pilot. Enrolment was expected to be between 30–300 women.

Ethical approval was obtained from the London School of Hygiene & Tropical Medicine (Ref: 15206) and Rawalpindi Medical University, Rawalpindi, Pakistan, prior to initiating the pilot study. Participants provided written informed consent to participate. We recorded research findings using the draft questionnaire, cognitive interview questionnaire, and a daily debriefing form.

Phase 2: Modification and pilot testing

Step A: An expert panel of four local obstetricians at one hospital in Pakistan reviewed and modified the questionnaire and translated it into Urdu. The questionnaire was reviewed by a group of women soon after they had given birth and modified, and then tested on individual patients over three days.

Cognitive interviews explored participant understanding of questions and answer choices, whether participants understood the questions, whether they were able to say in their own words what the question was asking and any suggestions for improving the questions. Qualitative data were analysed at the end of each day and the questionnaire modified accordingly.

Step B: A final version of the questionnaire[16] was developed, translated, and printed into Urdu and English. This was tested between April and July 2018 at the hospital.

Phase 3: Quantitative analysis of pilot study

Step A: Descriptive statistics were used to describe background characteristics of the study population. Scores for the relevant domains were calculated for each participant. T-tests, Z-tests, linear and logistic regression (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) were used to explore the data and examine the association between how women reported their health and well-being and a) if they experienced PPH and b) if they had severe anaemia.

Step B: We examined the quantitative and qualitative results of the study and decided on the final conceptual framework and questionnaire for inclusion in the WOMAN-2 trial.

Results

Raw data for this study are available from LSHTM Data compass following free registration[16].

Phase 1: Initial conceptual framework and questionnaire design

Step A: The outline set of questions sought participant reported perspectives on breastfeeding, symptoms of anaemia, feelings, and ability to do daily activities. The new mothers PPI group noted the following: asking about the mother's health and well-being would be welcomed, as immediately after birth much attention is focused on the baby, rather than the mother; the importance of keeping the questionnaire as short as possible; and that new mothers are worried about if they will be able to care for and feed their baby properly.

Step B: Further review of the literature identified the Multidimensional Fatigue Symptom Inventory-short form (MFSI-SF)[17,18], which was initially developed as a measure for cancer patients, and has been applied in different disease areas[19]. The MFSI-SF provides a composite score for multidimensional fatigue and includes scores for the test's five component domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigour. This measure has been shown to have good psychometric properties, has been validated, and is recommended for use in studies[19]. We chose to test this instrument because of successful use in previous trials, and because it includes many of the domains we were interested in measuring, such as fatigue, energy levels, and feelings. Although the recall time and wording of the tool was not written for women who had recently given birth, the MFSI-SF was selected as an appropriate tool to adapt and test in this pilot study.

Phase 2: Modification and pilot testing

Step A: Key feedback on the draft questionnaire raised by the expert team of four local obstetricians included: women will be tired so questions should be kept short; many participants will have little education or be illiterate; and use of visual scales is not generally understood in this population. The overall structure of the questionnaire was kept, with slight modifications made to questions and answer choices. For the MFSI-SF, vernacular wording in the questions was first translated into more understandable English for international use, and then translated into Urdu.

Feedback froman initial group of six participants included: the set of questions about physical and mental abilities and feelings

due to fatigue were inappropriate for them because these were primarily affected by pain; and answer responses should be short, simple, and consistent across the entire questionnaire, as was used in the MFSI-SF section. Participants discussed their experiences of having anaemia. Symptoms of anaemia stated by participants included: breathlessness, dizziness, shaky hands, feeling tired, feeling faint, heart palpitations, body aches and pains, and numbness. Due to these symptoms, some women reported being worried about themselves and their ability to take care of their children. Questionnaire changes included removal of questions asking about abilities and feelings due to fatigue; addition of a global question on pain; addition of a global question on wellness; addition of questions about anaemia symptoms for: feeling sleepy, feeling numbness, feeling of shaky hands; removal of all visual scales; and modification of all response choices to be consistent with the response choices used in the MFSI-SF. Important implementation factors learned at the review meeting were to conduct interviews in the morning, before hospital discharge, and to interview patients alone, with no relatives present.

Over three days, nine women participated in the portion of the pilot study which included cognitive interviews. Questionnaire administration and cognitive interviews revealed issues of clarity with question wording and translations. Changes to the questionnaire and translation were made continuously until participants easily understood the question meanings. For the MFSI-SF, it was necessary to add "since giving birth until now" to clarify the time period the question was referring to. This was because participants were not sure if the questions were referring to a period which included their pregnancy or not. Many of the questions also needed the additional clarification of "taking into account everything…" before the question. This was added to help participants focus on the overall nature of the question. For example, some participants had competing feelings, such as feeling elated for having a first baby, but deeply sad and worried since their baby had been taken to the intensive care unit. Once this phrase was added to the questions, participants were able to understand its meaning and more easily answer. Table 1 provides a comparison between the MFSI-SF and the adapted version for this pilot study. In addition to the changes mentioned above, clear instructions with a simple example were added at the beginning to introduce the process. Interviews were best conducted in the mornings, when women could lay in their beds and be more comfortable for the duration of the interview.

Step B: The final pilot questionnaire contained six domains and 41 questions. The six domains included: multidimensional fatigue (MFSI-SF: 30 questions), symptoms of anaemia (7 questions: dizziness, headache, heart beating fast/racing, feeling sleepy, numbness in hands and feet, shaky feeling in hands, difficulty breathing), statement of feeling ill (1 question), statement of feeling pain (1 question), statement about difficulty breastfeeding (1 question), and perception of expected ability to do usual activities once home (1 question). Each of the 41 questions had the same five response choices: not at all, a little, moderately, quite a bit, extremely.

Phase 3: Quantitative analysis of pilot study and finalisation of questionnaire

Step A: Baseline characteristics of the pilot study population are provided in Table 2. A total of 124 women were enrolled in the final pilot study, ranging in age from 18–38 years. All participants had anaemia, with 23% having severe anaemia (<7 g/dl); 31.5% of the study population experienced a PPH.

Score calculations. The MFSI-SF scores were calculated as per instructions from the MFSI-SF tool[18,20]. An overall anaemia symptoms score was calculated by adding the scores of seven separate anaemia symptom questions. Illness, pain, and expected ability to do usual activities were single questions. Because many women who experienced a PPH were not able to breastfeed, this information was combined with the question about difficulty breastfeeding by adding a score "worse" than "extremely" on the difficulty scale for women who were not breastfeeding.

For analyses examining illness, pain, expected ability to do usual activities, and breastfeeding, responses were categorised into two groups: those answering "not at all", "a little" or "moderately" or those answering "quite a bit" or "extremely" (with breastfeeding having one additional "worse" score after "extremely" to reflect not breastfeeding).

Figure 2a, b shows there is strong evidence that participants who experienced PPH compared to those who didn't experience PPH, and those with severe anaemia compared to those with moderate anaemia, answered questions on the MFSI-SF differently, with those experiencing PPH or severe anaemia having higher scores, indicating they felt more fatigue. Figure 2c, d shows there is strong evidence that participants who experienced a PPH compared to those who didn't experience a PPH, and those with severe anaemia compared to those with moderate anaemia, reported more symptoms of anaemia. Similar results examining the same relationships, via multiple linear regression, are reported in Table 3.

Adjusted analyses of subdomains within the MFSI-SF showed strong evidence that participants with PPH and participants with severe anaemia scored "worse" on different measures for fatigue ((general, physical, emotional, mental (severe anaemia only)) and vigour (PPH only) (Table 3).

The pilot study results indicate that participants who experienced a PPH, when adjusted for severe anaemia, reported feeling more ill than participants without PPH (Table 3). When considering reported difficulty breastfeeding together with not breastfeeding, women who experienced a PPH, when taking into account severe anaemia, reported more difficulty or "inability" to breastfeed.

In this analysis, there was no evidence of an association between reporting pain and experiencing PPH or severe anaemia (Table 3). There was also no evidence of an association between reporting an expectation of difficulty of doing usual activities when going home and experiencing PPH or severe anaemia (Table 3).

Table 1. Differences between Multi-dimensional Fatigue Symptom Inventory, Short Form (MFSI-SF) and modified MFSI-SF for WOMAN-2 Pilot.

Item Number	MFSI-SF	MFSI-SF Adapted for Woman-2 Pilot
	Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes how true each statement has been for you in the past 7 days.	**I am going to read some statements to you that describe how people sometimes feel. Each question has five possible answers. Please tell me which answer best describes how you feel since having your baby until now.** **I will give you an example:** **I will say "I feel hungry right now" and I want you to tell me which of the following answers best describes how hungry you feel right now. The options are not at all, a little, moderately, quite a bit, extremely.** **What answer would you give? (allow the patient to answer)**
1.	I have trouble remembering things	Since giving birth until now I have trouble remembering things
2.	My muscles ache	Since giving birth until now, my muscles ache all over my body
3.	I feel upset	Taking into account everything since giving birth until now, I feel upset
4.	My legs feel weak	Since giving birth until now, my legs feel weak
5.	I feel cheerful	Taking into account everything since giving birth until now, I feel happy (cheerful)
6.	My head feels heavy	Since giving birth until now, my head feels heavy
7.	I feel lively	Taking into account everything since giving birth until now, I feel happy to do things with energy (feel lively)
8.	I feel nervous	Taking into account everything since giving birth until now, I feel nervous or uneasy
9.	I feel relaxed	Taking into account everything since giving birth until now, I feel relaxed
10.	I feel pooped	Since giving birth until now, I feel too tired to continue (I feel pooped)
11.	I am confused	Since giving birth until now, I am confused or I have difficulty understanding things
12.	I am worn out	Since giving birth until now, I am drained of energy (I am worn out)
13.	I feel sad	Taking into account everything since giving birth until now, I feel sad
14.	I feel fatigued	Since giving birth until now, I feel physically and mentally tired (fatigued)
15.	I have trouble paying attention	Taking into account everything since giving birth until now, my mind is wandering around (I have trouble paying attention)
16.	My arms feel weak	Since giving birth until now, my arms feel weak
17.	I feel sluggish	Since giving birth until now, I feel physically slow (sluggish)
18.	I feel run down	Since giving birth until now, I feel in a bad state (I feel run down)
19.	I ache all over	Since giving birth until now, I ache all over
20.	I am unable to concentrate	Taking into account everything since giving birth until now, I have trouble focussing on things (I am unable to concentrate)
21.	I feel depressed	Taking into account everything since giving birth until now, I feel depressed
22.	I feel refreshed	Taking into account everything since giving birth until now, I feel refreshed or fresh
23.	I feel tense	Taking into account everything since giving birth until now, I feel tense
24.	I feel energetic	Since giving birth until now, I feel energetic or have energy to do things
25.	I make more mistakes than usual	Since giving birth until now, I make more mistakes than usual
26.	My body feels heavy all over	Since giving birth until now, my body feels heavy all over
27.	I am forgetful	Since giving birth until now, I am forgetful
28.	I feel tired	Since giving birth until now, I feel physically tired
29.	I feel calm	Taking into account everything since giving birth until now, my mind is at peace (I feel calm)
30.	I am distressed	Taking into account everything since giving birth until now, I am as very worried (distressed)

Table 2. Study population characteristics.

Description of pilot study population	
Number of participants	124
Characteristics at baseline	N (%)
Mean age (range)	27 (18–38)
Education level: some secondary education or above, n (%)	57 (46.3)
Median parity (range)	2 (1–8)
Birth canal trauma, n (%)	4 (3.2)
Uterine rupture, n	0
Post-partum haemorrhage, n (%)	39 (31.5)
Severe anaemia, n (%)	28 (22.6)
Laparotomy, n	0
Manual removal of placenta, n	0
Evacuation of retained products of conception, n (%)	39 (31.5)
Of women having ERPC, those also having PPH, n (%)	33 (26.6)
Transfusion (blood product), n (%)	44 (35.5)
Hysterectomy, n	0
Cardiovascular dysfunction, n	0
Respiratory dysfunction, n (%)	1 (0.8)
Renal dysfunction, n (%)	2 (1.6)
Coagulation/dysfunction, n (%)	4 (3.2)
Hepatic dysfunction, n (%)	1 (0.8)
Neurological dysfunction, n	0
Sepsis, n (%)	10 (8.1)
Post-partum eclampsia, n (%)	1 (0.8)
Baby died at this birth, n (%)	23 (18.6)

Step B: A final analysis included consideration of the qualitative and quantitative results, pilot study implementer feedback, and objectives of the questionnaire in relation to the WOMAN-2 Trial. It was decided that the final pilot version of the conceptual framework (Figure 3) and the final version of the questionnaire were suitable for assessing health and well-being outcomes in the WOMAN-2 trial.

Discussion

The purpose of this study was to develop a conceptual framework and PRO questionnaire to measure maternal health and well-being outcomes for the WOMAN-2 trial. Our conceptual framework and questionnaire were developed through literature reviews, expert consultation, PPI consultation, and an iterative process of pilot testing questions with anaemic women in Pakistan who had just given vaginal birth and experienced different birth outcomes.

Limitations

A limitation of this study is that we pilot tested the questionnaire at one hospital in Pakistan, while the clinical trial will be carried out in multiple hospitals in Pakistan, Nigeria and Uganda. The hospital where the pilot was conducted draws from a population that may be more urban and affluent than other areas where the trial will be conducted. Due to the pragmatic nature of the pilot study, we enrolled 124 participants and were only able to translate and test the questionnaire in Urdu. The questionnaire for the clinical trial will ideally need to be tested and translated for use in other countries and other languages.

Multifaceted and iterative process

We used a multifaceted and iterative approach to develop our conceptual framework and PRO questionnaire. We consulted new mothers about their concerns after giving birth, and what measures would be important to include in assessing maternal health and well-being. We also consulted topic experts. Through our pilot study we modified questions and response choices until they were simple, clear, and easily understood by respondents. Language was an important factor for consideration, as different individuals can assign different meaning to the same words. We used the committee method of translation, rather than forward and backward translation, to ensure that the whole team agreed

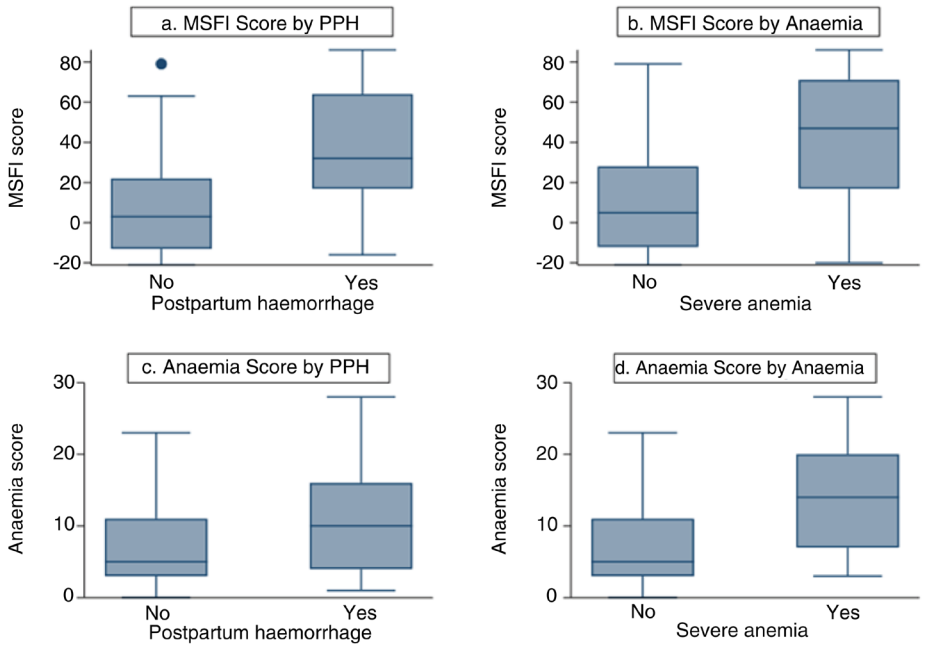

Figure 2. Multi-dimensional Fatigue Symptom Inventory, Short Form (MFSI-SF) and anaemia scores by postpartum haemorrhage and severe anaemia. PPH, postpartum haemorrhage.

Table 3. Association of PPH and severe anaemia on pilot questionnaire domains.

Association of PPH and severe anaemia on pilot questionnaire domains						
Association of PPH and severe anaemia on MFSI total score*						
	Crude coefficient	**95 %CI**	**P value**	**Adjusted coefficient**	**95 %CI**	**P value**
PPH vs. no PPH	27.88	17.85-37.91	0.000	19.88	8.55-31.21	0.001
Severe anaemia vs. moderate anaemia	28.72	17.40-40.05	0.000	17.54	4.96-30.12	0.007
Association of PPH and severe anaemia on **general** domain score within MFSI*						
PPH vs. no PPH	7.04	4.19-9.89	0.000	4.91	1.67-8.14	0.003
Severe anaemia vs. moderate anaemia	7.45	4.25-10.64	0.000	4.69	1.10-8.28	0.011
Association of PPH and severe anaemia on **physical** domain score within MFSI*						
PPH vs. no PPH	5.52	2.68-8.36	0.000	3.90	0.64-7.16	0.019
Severe anaemia vs. moderate anaemia	5.73	2.56 8.91	0.001	3.54	−0.080-7.16	0.055
Association of PPH and severe anaemia on **emotional** domain score within MFSI*						
PPH vs. no PPH	6.45	4.25-8.65	0.000	4.81	2.32-7.31	0.000
Severe anaemia vs. moderate anaemia	6.29	3.77-8.81	0.000	3.58	0.81- 6.36	0.012
Association of PPH and severe anaemia on **mental** domain score within MFSI*						
PPH vs. no PPH	3.11	1.02-5.20	0.004	1.30	−1.05-3.65	0.275
Severe anaemia vs. moderate anaemia	4.69	2.44-6.95	0.000	3.96	1.35-6.57	0.003
Association of PPH and severe anaemia on **vigour** domain score within MFSI*#						
PPH vs. no PPH	-5.76	−7.62-−3.91	0.000	-4.96	−7.10-−2.81	0.000
Severe anaemia vs. moderate anaemia	-4.56	−6.77-−2.35	0.000	-1.77	−4.15-0.61	0.143

Association of PPH and severe anaemia on pilot questionnaire domains						
Association of PPH and severe anaemia on MFSI total score*						
	Crude coefficient	**95 %CI**	**P value**	**Adjusted coefficient**	**95 %CI**	**P value**
Association of PPH and severe anaemia on **anaemia symptoms** score*						
PPH vs. no PPH	4.02	1.52-6.51	0.002	1.67	–1.11- 4.45	0.236
Severe anaemia vs. moderate anaemia	6.08	3.41-8.74	0.000	5.14	2.05-8.22	0.001
Association of PPH and severe anaemia on whether women answered "quite a bit or extremely" vs. "not at all, a little, moderately" regarding having **pain** right now+						
PPH vs. no PPH	1.75	0.56-5.44	0.334	2.18	0.60-7.92	0.236
Severe anaemia vs. moderate anaemia	0.93	0.254-3.58	0.913	0.60	0.13-2.78	0.510
Association of PPH and severe anaemia on whether women answered "quite a bit or extremely" vs. "not at all, a little, moderately" regarding **feeling ill** right now+						
PPH vs. no PPH	6.39	2.62-15.59	0.000	4.39	1.61-11.98	0.004
Severe anaemia vs. moderate anaemia	5.00	2.00-12.48	0.001	2.38	0.82-6.87	0.109
Association of PPH and severe anaemia on whether women answered "quite a bit or extremely" vs. "not at all, a little, moderately" regarding whether they think they will have difficulty doing their **usual activities** after returning home+						
PPH vs. no PPH	2.18	0.96-5.00	0.062	1.70	0.67-4.29	0.260
Severe anaemia vs. moderate anaemia	2.42	0.94-6.25	0.068	1.82	0.62-5.30	0.273
Association of PPH and severe anaemia on whether women answered "quite a bit or extremely" (or were not breast feeding) vs. "not at all, a little, moderately" regarding having **difficulty breastfeeding** my baby+						
PPH vs. no PPH	3.45	1.57-7.61	0.002	2.58	1.05-6.33	0.039
Severe anaemia vs. moderate anaemia	3.24	1.36- 7.74	0.008	1.96	0.72-5.33	0.186

* Effect estimates are calculated using linear regression

Lower scores denote being better off (opposite direction of other domains within MFSI)

+ Effect estimates are calculated using logistic regression

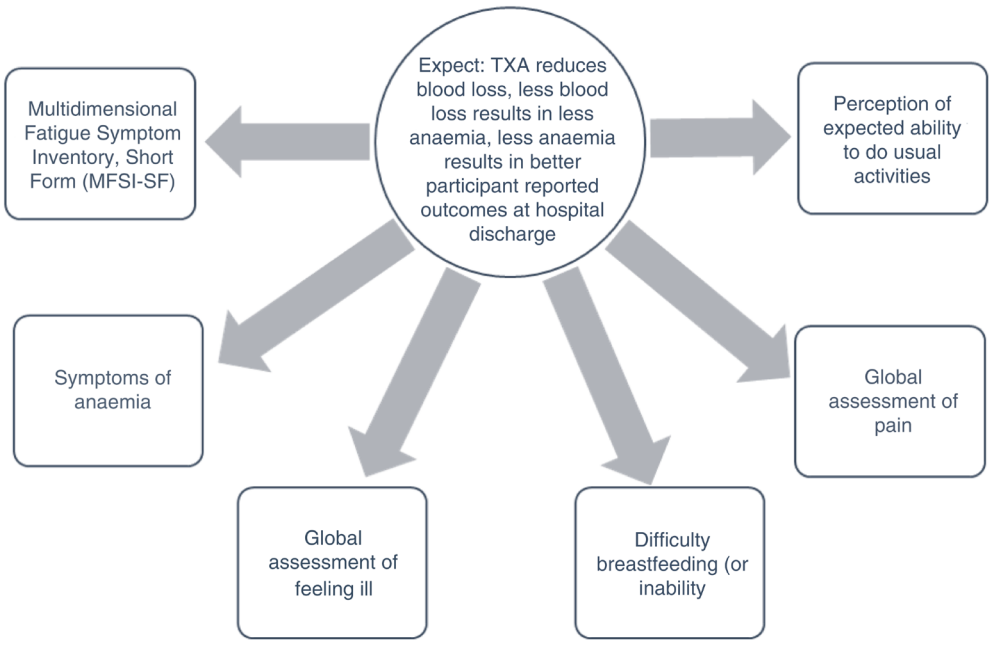

Figure 3. Conceptual framework.

translations were accurate and would be understood in the same way in both English and Urdu. Results of our four-month pilot study with 124 participants showed that the questionnaire was easily understood by participants and had a 20-minute implementation time. These features are important for our population who are likely to be within hours or a few days of giving birth, and are therefore tired and in pain, with attention focused on their babies. Based on these findings, we believe the final questionnaire piloted in this study is acceptable and relevant to mothers, and feasible to implement in busy maternity wards.

Quantitative results

We examined the association between how women reported their health and well-being in six different domains and if they had experienced a PPH or severe anaemia.

MFSI, anaemia, feeling ill, breastfeeding. We found that women who experienced a PPH or had severe anaemia were more likely to report poorer outcomes with respect to the total MFSI-SF score, indicating that those women experienced statistically significant more fatigue. Although we did make modifications to the recall time and wording of the validated tool, the questionnaire performed well for our purposes and was sensitive enough to detect differences in multidimensional fatigue in our population. As expected, women who had severe anaemia reported more severe symptoms of anaemia compared to women with moderate anaemia. This demonstrates that our set of questions are able to detect differences in symptoms which are important to women. Our results showed that women who experienced a PPH or were severely anaemic were more likely to report feeling ill. In our study, 39 women experienced a PPH, of which 23 were not breastfeeding at the time of the questionnaire. For our analysis examining the associations of PPH and severe anaemia on breastfeeding, we chose to combine the two most difficult levels of breastfeeding with not breastfeeding to more accurately reflect the effect a PPH or severe anaemia might have on a woman's ability to breastfeed. Based on results of this pilot study, for the WOMAN-2 trial, we will include an additional question about why the participant is not breastfeeding, so we can exclude women who have specific reasons why they are not breastfeeding which are unrelated to the effects of PPH or anaemia.

Pain, expected ability to do usual activities once home. Based on discussions with participants, we understood that pain was a symptom which was affecting their well-being immediately after childbirth. Our results did not show that women who experienced a PPH or had severe anaemia reported more pain. This may be because pain is common across all postpartum women and may not be affected by PPH or anaemia. We decided to keep this question in the final questionnaire for the clinical trial because this outcome was identified as important to participants and may impact physical abilities such as walking which is being assessed in the trial. Our question about expected difficulty to do usual activities once home also did not show that women who experienced PPH or severe anaemia answered that question differently than women who did not experience PPH or had moderate anaemia. This result could be because the effects of a PPH or severe anaemia were not such to warrant women stating they expected more difficulty to do their usual activities. Alternatively, this result might be due to specific cultural circumstances: families in the area of our pilot study typically expect a postpartum woman to rest, while female family members take care of chores. This cultural practice may not be the case in other populations where the WOMAN-2 trial will be conducted, or where populations are less affluent. Another possible explanation is that this question, unlike other questions, asks a woman to anticipate her future situation. Women may answer this question based on their hopes, rather than on their realities or their fears. For these reasons and because women shared with us their concerns about being able to take care of their children, we chose to keep this question in the final questionnaire for the WOMAN-2 trial.

Conclusion

We have developed a conceptual framework and PRO questionnaire to measure how blood loss affects anaemic women's health and well-being. Our iterative and multi-faceted approach, using qualitative and quantitative methods, has allowed us to develop a questionnaire which measures health and well-being outcomes important to mothers, which is clear and acceptable to women in the immediate postpartum period, and which has demonstrated sensitivity with respect to detecting differences in how women who experience PPH or severe anaemia answer questions. The final conceptual framework and questionnaire used in our pilot study will be included in the WOMAN-2 trial to be conducted in Pakistan, Nigeria, and Uganda.

Data availability

Underlying data

The anonymised data used for the quantitative analysis is available from the freeBIRD data portal at https://freebird.lshtm.ac.uk/index.php/data-sharing/downloads/woman-2-pilot-study/ following free registration: DOI https://doi.org/10.17037/DATA.00001109[16].

Extended data

The full questionnaire generated for the study is available from the freeBIRD data portal at https://freebird.lshtm.ac.uk/index.php/data-sharing/downloads/woman-2-pilot-study/. following free registration: DOI https://doi.org/10.17037/DATA.00001109[16].

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 29 July 2019

https://doi.org/10.21956/wellcomeopenres.16640.r35899

✓ **Joshua P. Vogel**
Maternal and Child Health Program, Burnet Institute, Melbourne, Australia

Authors aimed to develop a tool for measuring women's perceptions of health impacts of postpartum blood loss. They have conducted a literature review, qualitative research and pilot testing with postpartum women with anaemia in Pakistan (interviews and questionnaire completion) to develop this tool. They describe multiple cycles of consultation and tool development with a patient and public involvement group in the UK, obstetricians and women in Pakistan. The tool will be used to assess patient's perspectives in a forthcoming trial of tranexamic acid for PPH prevention in high-risk women (women with anaemia).

Findings highlight that there are key differences in how participants reported their health and well-being when they had experienced a PPH or severe anaemia, highlighting the need for a tool specific to this population. It is to my knowledge novel and a useful piece of research to understanding and measuring women's experiences around blood loss, particularly for women with anaemia which is prevalent in many countries.

Major comments:

- The authors acknowledge that use of the tool in other countries/languages in the WOMAN trial will ideally require further evaluation. Given the domains of the tool itself, one would reasonably expect that concepts such as pain, activities of daily living and feeling ill would vary between settings. However, the concluding section indicates the tool will be used as it is in the other countries - clarification on whether further evaluation/adaptation is going to be done or not would be helpful.

- Tool was translated into Urdu, however no mention is made of back-translation/verification. Would be helpful to know how translation was verified.

- Please clarify how the sample sizes were arrived at (9 women for interviews, 124 women for pilot test).

Minor comments:

- Under Phase 2: modification and pilot testing - change "Feedback froman initial group" to

"from an"

Is the rationale for developing the new method (or application) clearly explained?
Yes

Is the description of the method technically sound?
Yes

Are sufficient details provided to allow replication of the method development and its use by others?
Yes

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions about the method and its performance adequately supported by the findings presented in the article?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Maternal and perinatal health research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 03 June 2019

https://doi.org/10.21956/wellcomeopenres.16640.r35608

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Shireen Meher
[1] Department of Women's and Children's Health, University of Liverpool, Liverpool, UK
[2] Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[3] Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

The purpose of this study was to develop a conceptual framework and questionnaire to measure the participant reported outcome of maternal health and well-being in the context of PPH in anaemic women for the WOMAN-2 trial. This was developed through literature reviews, expert consultation, PPI consultation, and an iterative process of pilot testing questions with postnatal anaemic women in Pakistan. The performance of the questionnaire was assessed in women who had or had not experienced a PPH and those who had moderate vs severe anaemia.

This is a very interesting piece of research in an area that is often understudied (patient reported outcomes) and is novel in that no similar tools to capture PROs exist in the area of PPH. I commend the authors for undertaking this very important work and doing it through a rigorous methodical process.

There are limitations to this work - the very obvious one is the limited generalisability of the findings (participants came from a single country and spoke a single language) but this has been acknowledged. It is unclear if further work is planned to refine this questionnaire in other countries as the authors state it will 'ideally need to be tested and translated in other countries and other languages'. The validity of this work would increase significantly if this was actually done.

Specific comments:

A. Aspects of the methods need further clarification/detail:

1. How were domains developed/defined?
2. What was the purpose of the additional literature review and why was it needed when an initial literature review had been done previously?
3. Who was in the team for team discussions and which experts in what field were consulted?
4. Eligibility criteria states women had to be anaemic and within 42 days of delivery. Please clarify:
   - What was the time gap between blood test to confirm anaemia and date of interview, as women may have been on iron tablets to correct the anaemia and if there was a long gap this may impact results.
   - 42 days is a long time, and it would be helpful to add further information on how many days postnatal the women who were interviewed actually were as this will impact on recall.
5. I am unclear as to why the authors chose to remove questions about abilities and feelings due to fatigue instead of modifying them to make them more acceptable questions. My worry is that the acceptability of these questions may have also been influenced by cultural practices/beliefs.
6. Definition of severe anemia needs to be moved to earlier in methods and not be first presented in the results.

B. Conclusions - the authors state the questionnaire is acceptable to women - what this formally assessed i.e, were women asked this question? If not, then perhaps this statement should be removed.

Is the rationale for developing the new method (or application) clearly explained?

Yes

Is the description of the method technically sound?

Yes

Are sufficient details provided to allow replication of the method development and its use by others?

Partly

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions about the method and its performance adequately supported by the findings presented in the article?
Partly

Competing Interests: I led the research on development of Core Outcomes Sets for PPH.

Reviewer Expertise: PPH, Core Outcome Sets, pre-eclampsia, systematic reviews and RCTs.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 Apr 2021

Haleema Shakur-Still, London School of Hygiene & Tropical Medicine, London, UK

Comment: How were domains developed/defined?

Response: We have updated the manuscript and added more details to explain our iterative process which explored domains of health and well-being that were stated in the literature, were important to new mothers, and that we could measure using a PRO tool appropriate for administration just after women have given birth.

Comment: What was the purpose of the additional literature review and why was it needed when an initial literature review had been done previously?

Response: The development process of the PRO was iterative. We have added more text to explain this and that there was an initial review of the literature to identify relevant domains of health and well-being for postpartum anaemic women and to identify existing questionnaires, and that a further search was conducted after receiving feedback from the new mothers group.

Comment: Who was in the team for team discussions and which experts in what field were consulted?

Response: The team consisted of a clinical trialist/nurse, an obstetrician with qualitative research experience and four senior experienced obstetricians.

Comment: Eligibility criteria states women had to be anaemic and within 42 days of delivery. Please clarify:
- What was the time gap between blood test to confirm anaemia and date of

interview, as women may have been on iron tablets to correct the anaemia and if there was a long gap this may impact results.
- 42 days is a long time, and it would be helpful to add further information on how many days postnatal the women who were interviewed actually were as this will impact on recall.

Response: We asked for the haemoglobin level or packed cell volume prior to delivery recorded at this hospital admission. If that was not available, we accepted any pre-delivery value that was most recent prior to giving birth on this occasion. However, in all cases, the Hb value immediately prior to giving birth was available.

A time frame of 42 days was chosen as this is traditionally considered to be the postpartum period. However, as all interviews took place prior to discharge after giving birth, the time gap was typically within 24 hours of giving birth. It is unlikely that any treatment with iron tablets in this short period could influence the results.

Competing Interests: Author's response