

BMJ Open

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Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012592
Article Type:	Research
Date Submitted by the Author:	11-May-2016
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Primary Subject Heading:	Qualitative research
Secondary Subject Heading:	Complementary medicine
Keywords:	clinical trial participation, motivation, financial compensation, treatment options, dysmenorrhea

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Women's reasons to participate in a clinical trial for menstrual pain – a qualitative study**Running title:** Women's reasons for trial participationSusanne Blödt¹, Claudia M Witt^{1,2}, Christine Holmberg³¹ Institute for Social Medicine, Epidemiology and Health Economics, Charité -
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Keywords: clinical trial participation, motivation, financial compensation, treatment options,
dysmenorrhea**Word count:** abstract: 369; text: 3858

ABSTRACT

Objectives: The aim of the study was to explore women's motivations to participate in clinical trials and to evaluate how a financial compensation has an impact on women's explanations for participation in clinical studies.

Design, setting and participants: Semi-structured with 25 out of 220 women who participated in an app-administered self-care acupuncture for dysmenorrhea (AKUD) study, a pragmatic randomized controlled trial were conducted face-to face or by telephone. Of these women 10 had entered AKUD knowing that they would receive a financial compensation of €30.

A purposive sampling strategy was used.

Results: Women had a long history of seeking help from their physicians and were unsatisfied with the options available, namely painkillers. While all interviewees were open to painkillers, they were uneasy about taking them on a monthly basis. The AKUD trial offered the possibility to find an alternative solution. A second reason for participation was the desire to add a new treatment into routine medical care, for which the interviewees considered randomized controlled trials a prerequisite. Although the financial incentive accelerated the recruitment process, it was a subsidiary motivation in the interviewees' narratives.

Conclusion: Our results contribute to the ongoing discussion of the impact of financial compensation on research participants' assessment of risk. Interviewed women's assumed that trial participants are able to assess the risks and benefits of participation and make voluntary choices, even when financial compensation is a factor in the decision-making process. Furthermore, the importance of clinical trials providing new treatments that could change medical practice might be an overlooked reason for trial participation, and could be used as an argument in future recruitment strategies.

Strengths and limitations of the study

- The special setting of our study that included both women who had entered the clinical trial knowing and not knowing that they would receive a financial compensation of €30 allowed us to focus on the role of financial compensation in the decision making process of women deciding on trial participation.
- Our results show the importance women placed on changing medical practice through their trial participation.
- Our sample was predominantly highly educated including many with a medical background.
- AKUD is a clinical trial with very low risk without medication intake.

INTRODUCTION

Randomized clinical trials are seen as the gold standard in clinical research, yet their success depends on the willingness of people to volunteer. Poor recruitment for clinical studies impacts statistical power, internal and external validity, and can cause financial and practical restrictions.¹ Recruitment problems are a common obstacle in clinical studies^{2,3} and numerous strategies have been identified to improve recruitment, including programs to increase potential participants' awareness of a health problem and its possible impact on them,⁴ making telephone contact with potential participants, and using opt-out rather than opt-in procedures.⁵ Campbell et al. found that certain factors proved successful in recruitment, including having a dedicated trial manager, it being cancer drug trial, and having interventions only available within the trial.⁶ Thus both trial characteristics and communication strategies with potential participants are of importance for recruitment.

The payment of research participants has also been shown to increase participation.⁷ Such a strategy is controversial, however, as it may unduly influence individuals' informed decision-making.⁵ In particular, it is argued that payment may unduly influence socioeconomically disadvantaged populations,⁸ and could jeopardize informed consent and participants' autonomous ability to properly assess risks and benefits.^{9,10} Indeed, studies have shown that higher compensation increases willingness to participate, and also that participants will assume higher risks when compensation is high.^{11,12} Whether it is ethical to pay research participants also depends on the purpose of payment.⁸ Ethical concerns do not generally affect studies with minimal risk of harm¹³ or those that reimburse only for time and travel expenses,⁹ but do arise when payments exceed a certain threshold and/or compensate for enrollment in risky studies.

To our knowledge, only one study to date has looked at research subjects' perspectives on financial compensation,¹⁴ with mixed results. Some of the unpaid participants argued that compensation is a valid recognition of participants; others clearly disagreed with the idea of paid participation, arguing that it is a moral duty. Altruism and the wish to benefit others and oneself have been identified as major reasons for participating in Phase III clinical trials,¹⁵⁻¹⁹ though given the evidence that communication strategies and trial characteristics might also be important motivations, the question arises of what altruism, moral duty and benefit to others actually imply. Indeed, it remains unclear how financial compensation actually influences participants' willingness to enroll in research, and what other factors also play a role.

In the pragmatic randomized acupuncture trial (AKUD)²⁰ the aim was to investigate the effectiveness of additional app-based acupressure compared to usual care for menstrual pain, recruitment was slower than anticipated. One means to increase participation was to introduce a financial compensation of €30 (the upper age limit for participants was simultaneously increased from 25 to 34 years). As a result of these changes the monthly recruitment figures for the AKUD trial almost doubled (mean

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3 n=13.4 per month after introduction of financial benefit compared to mean n=7 per month before
4 introduction of financial benefit).
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8 Within this existing setting, we nested the current qualitative study in order to analyze women's
9 motivations for participating in the clinical trial, including whether the small financial compensation
10 had an impact. Finally, we aimed to assess women's general views on financial incentives for research
11 participation.
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14 **METHODS**

15 **Design**

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17 This qualitative study was nested in the AKUD trial,²⁰ which ran from December 2012 to August
18 2014, and included 220 women with menstrual pain who were randomized into two groups: one for
19 additional app-based self-care acupressure (intervention) and a waiting list as a control group. Both
20 parts of the study were conducted by the Institute for Social Medicine, Epidemiology and Health
21 Economics at the Charité - Universitätsmedizin Berlin.
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27 The qualitative part consisted of qualitative, semi-structured interviews with trial participants after
28 completion of the quantitative part (lasting six menstruation cycles per individual). Based on
29 experience from other qualitative studies nested in randomized clinical trials, a sample size of 20-30
30 participants was aimed for.²¹⁻²³ The selected participants were invited to be interviewed by mail or
31 phone. Interviews took place at the institute, with the exception of the last four, which, due to
32 organizational reasons, were conducted by phone.
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36 The study was approved by the Charité - Universitätsmedizin Berlin Ethics Committee (28.08.2013 -
37 EA1/027/12).
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41 **Sampling and recruitment**

42 Recruitment for the qualitative study took place between September 2013 and January 2015 (21
43 interviews up to March 2014; 4 interviews between December 2014 and January 2015). The sampling
44 strategy was purposeful and the sample was selected based on whether the women had been recruited
45 to AKUD before or after financial compensation had been introduced, constituting two groups – 'non-
46 incentive' and 'incentive' respectively – and were further distinguished according to whether they had
47 been randomized to the intervention or to the waiting list.
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53 Participants were invited for the interviews after they were enrolled into the AKUD study. We planned
54 to interview at least 15 women from the non-incentive group and 10 women from the incentive group.
55 Recruitment ended after we had a sufficient number of interviewees from the incentive and the non-
56 incentive groups as well as from the intervention and the waiting list groups.
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Data collection

The interviews followed a guideline that had been developed based on the research question, existing literature and discussion within the study team. The guideline covered: the reasons why women had participated in the study; dealing with menstrual pain; decision-making for trial participation; views on financial compensation in clinical trials; and the use of an app as an intervention and data assessment tool. All interviews were conducted one-to-one by SB. To verify the findings of the analysis, four telephone interviews were conducted to ensure data saturation. All interviews were conducted only after written informed consent has been provided by interviewees.

At baseline we also collected women's socio-demographic data, data on menstruation, and reasons why they wanted to participate in AKUD (Table 1).

Table 1: Characteristics of the interviewees and the motivations to participate at baseline

	Recruitment without incentive <i>n=15</i>		Recruitment with incentive <i>n=10</i>	
	Intervention <i>n=4</i>	Control <i>n=11</i>	Intervention <i>n=9</i>	Control <i>n=1</i>
Mean age (M, SD)	23.3 ± 2.1	22.6 ± 2.0	26.6 ± 2.8	25
> 10 years of school education	3	11	9	1
In training	2	7	7	1
University degree	2	4	1	-
No educational training	0	0	1	-
Migration background	1	4	0	0
Painkiller against menstruation pain	4	8	6	1
Taking hormonal contraceptive	1	3	2	1
Worst pain during last menstruation (NRS: Mean, SD)	7.5 ± 1.0	7.0 ± 1.3	6.9 ± 0.9	8.0
Mean pain intensity during last menstruation (NRS: Mean, SD)	5.0 ± 2.2	5.3 ± 1.7	5.8 ± 1.6	7.0
Motivation to participate*				
Curiosity	0	8	4	0
Pain relief	4	10	8	1

Research contribution	0	7	4	0
No costs	0	0	2	0

* More than one answer was possible, financial compensation was not an answer option

Analysis

After each interview, the interviewer wrote a protocol that included interpersonal aspects of the interviews as well as brief summaries for each research question based on interviewees' statements. These interview protocols were included in the analysis to account for the relationship between interviewer and interviewee in data analysis.²⁴ The interviews were digitally recorded and transcribed verbatim. Transcripts were pseudomized using fake female names. Transcripts were uploaded into the software program MAXQDA (version 11 for Mac) and a thematic analysis of the transcripts was conducted.²⁵

All interview material was coded by SB. The first round of coding was done deductively using the interview guideline. Codes were: menstruation; pain experience and management; motivations for trial participation; decision-making process for trial participation; and opinions about financial compensation. After this initial thematic coding process, each coded segment was inductively coded based on the themes discussed. These two rounds of coding were conducted for the first five interviews.

The resulting codes and the coding tree were discussed by the research team; they were also discussed and analyzed in a qualitative research group to ensure intersubjectivity and grounding in the analysis. During these discussions, categories were developed and added. The first 21 interviews were coded accordingly. In this process, core themes emerged and were discussed by the research team. All analysis steps were documented in written memos. After 21 interviews, analysis was considered complete and results presented. To verify these results, four additional interviews were conducted.

RESULTS

Sample

Twenty-five women were interviewed, of which 15 were recruited to AKUD without financial incentive (non-incentive group; 4 intervention, 11 waiting list), and ten with financial incentive (incentive group; 9 intervention, 1 waiting list). The interviews lasted between 10 and 50 minutes. The characteristics of the interviewees and the baseline motivations to participate are displayed in Table 1. The mean age of the women in the non-incentive group was 22.7 years (range 21–25) and in the incentive group 26.4 years (range 24–33). The interviewees were mostly highly educated and one-third mentioned having a medical background (e.g., medical student, working at the Charité-Universitätsmedizin Berlin). One-third of women in the non-incentive group and none in the incentive

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3 group had a migration background. The majority ($n=19$) of interviewees took painkillers for their
4 menstrual pain, with ibuprofen, aspirin and paracetamol being the most common. Interviewees
5 suffered from severe pain, with a mean pain intensity (Numeric Rating Scale (NRS), 0=no pain,
6 10=worst possible pain) during last menstruation of 5.2 with a standard deviation (SD) of ± 1.8 for
7 women in the non-incentive group, compared to 5.9 ± 1.6 SD for the incentive group.
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12 Analysis of the interviews revealed that to understand women's participation in the AKUD trial, an
13 understanding of their prior situation was important, namely that they all routinely experienced a
14 significant impact of menstruation pain on their lives. All of the women had a history of finding an
15 appropriate solution and were unsatisfied with the options available, namely regular painkillers. While
16 all interviewees were open to painkillers, they were uneasy about taking them on a monthly basis.
17 Interviewees had an understanding that randomized clinical trials are a necessary prerequisite to
18 introducing a new treatment option into medical care. Although financial incentives accelerated the
19 recruitment process into AKUD, it was a subsidiary motivation in the interviewees' narratives.
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26 In the following, we describe the identified categories in detail. While analysis was conducted
27 separately for the incentive and non-incentive groups, results were similar. The findings are thus
28 presented jointly, except with regard to financial compensation.
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31 **Women's situation prior to trial participation**

32 *Impact of menstrual pain on interviewees' lives*

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34 All women described how menstruation pain impacted their daily lives and disturbed their normal
35 routines. For some, taking analgesics or the oral contraceptive pill alleviated the pain enough to allow
36 their activities to continue. Others discussed how the pain affected everything – social life, education,
37 work – and was all-encompassing while it endured; some had to stay in bed and avoid all activities
38 outside the house. Many interviewees described increased pain in stress situations and thus actively
39 tried to reduce stress during menstruation. Such coping strategies became problematic when
40 menstruation coincided with appointments that could not be postponed, while cancellation of
41 appointments and work absences caused additional emotional stress for some women. Sometimes, the
42 pain also ruined key planned events.
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50 *Yes, right, because it ... yes, menstrual pain is just stupid, it messes up everything, it always*
51 *comes when you have a birthday, or Christmas or when something is ... nice actually, and then*
52 *it's always so annoying when then ... you just lie in bed the whole time, or have to take a whole*
53 *lot of painkillers (non-incentive, intervention group).*
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57 *Dealing with menstrual pain*

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3 All interviewed women except for three regularly took analgesics to reduce menstrual pain. They took
4 between one and 3 to 4 pills per day over the course of three days. Of the three women who were not
5 taking regularly painkillers, they addressed their pain by lying down with a hot water bottle and one
6 took contraceptive pills specifically to reduce her menstrual pain; all three reported that their pain was
7 manageable without painkillers as a result. Another woman took contraceptive pills against menstrual
8 pain, but wasn't able to alleviate the pain with painkillers.
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13 The women were not against medication in general, though they did perceive them critically due to the
14 potential side effects. They also did not think that alternative medicine is better than usual medicine.
15 Nevertheless, they shared a critical view on analgesics as a regular solution for menstrual pain. The
16 regularity and continuity of menstruation and the related pain, as mentioned by five women ($n=2$ non-
17 incentive; $n=3$ incentive), made it difficult to accept analgesia as an appropriate solution.
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23 *So it was for me perhaps already the primary decisive reason ... because I thought maybe it*
24 *helps somehow. And because it always bothered me that I have to take so many painkillers. If*
25 *once a month you always have to take so many painkillers ... actually I do not like the feeling*
26 *(incentive, intervention group).*
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30 For some interviewees, therapies such as analgesics and contraceptives that had been offered by their
31 health care providers were ineffective as pain relief or had not been tolerated ($n=4$ non-incentive; $n=4$
32 incentive). Many of the participants had sought alternatives to analgesics – including household
33 remedies such as hot water bottles and tea – but with limited success. Some participants had tried, with
34 mostly minimal effect, acupuncture, herbs, homeopathy, dancing/movement and gymnastics. Such
35 experiences left women feeling alone with their complaints and disillusioned with the medical system.
36 The AKUD trial offered the possibility to find a solution.
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40 While most women mentioned time investment as a factor for deciding to participate in AKUD, the
41 most important reason was the monthly ordeal they experienced, for which they only knew medication
42 remedies that made them feel uncomfortable.
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48 ... Um ... yeah! so it's just as I said. I'm sick once a month and I find that quite a limitation
49 given the fact that it's not a disease. ... And uh, I just hoped that something could help. That I
50 could just ... cope with my everyday life. ... Because up till now there has been no solution
51 *(incentive, intervention group).*
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56 Women on the waiting list therefore did not mind waiting, since it did not imply anything worse that
57 what they normally experienced.
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Desired effects of trial participation

Adding a treatment option to medical care

In addition to finding relief for their own monthly pain, some interviewees clearly indicated that their participation could benefit other women, as a positive evaluation of acupuncture would lead to more treatment options that physicians could offer their patients. Such ideas were coupled with their belief that menstrual pain and dissatisfaction with current therapeutic options are an experience shared by many women.

Women considered their study participation an important part of building evidence for medical practice. Because they assumed that the trial results would help change medical practice, they were also open to the procedure of randomization as a means to obtain valuable scientific evidence. Interviewees likewise emphasized the importance of informing gynecologists if the results of the study were positive, in the hope of reaching as many women as possible.

Exactly, it is of course that; I hope, or I wish also, uh, that it somehow turns out that acupuncture somehow is a very big success, and that it might be a real option. ... so for me the study proved really meaningful and you could say ... okay, women have ... such and such a percentage somehow to thereby have an improvement or so. ... And then you could, maybe you can actually publish that and can say, okay ... try this ... (non-incentive, waiting list group).

Financial benefit

Although financial gain could not have been a motivation for participation for the 15 women in the non-incentive group, all of the women in both groups expressed gratitude for the financial compensation (those in the non-incentive group also received the €30 after the financial benefit had been introduced). The majority agreed that financial compensation to cover transportation and time expenditure is appropriate for the efforts of trial participation. Only two women in the non-incentive group argued that the potential personal benefit outweighed any time expenditure and found financial compensation unnecessary.

Yes exactly. I see no reason, actually, no reason uh: that you pay us for it [participation]. ... Because ... uh, the people who participate gladly take the time for it and ... are not forced into it, so ... I don't know. For me it goes without saying that when there is actually no money, that it is not about money. Because uh: you give us something. So we, we give our time, but we usually get a positive result, so ... (non-incentive, waiting list group).

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3 Some women in the incentive group did argue that financial compensation had been a deciding factor
4 for participation. The majority of interviewees were students or in vocational training, and they
5 mentioned (n=2) the importance of a small subsidy for daily expenses.
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9 *Um: -...- on the other hand, even if, if it's not much money, it's just still the thirty Euros that we*
10 *as trainees, we're just ... always at the limit anyway. Yes, still not a lot of money and then doing*
11 *it also for thirty Euros is also ... a trifle.*

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13 *I: Hmm, hmm. That was, so that was also something extra, it was an added incentive.*

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15 *Thea: Yes (incentive, intervention group).*
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18 Overall, interviewees believed that clinical trials are necessary to improve medical practice. Thus
19 payment to incentivize recruitment is also necessary, since without it medical progress could be
20 endangered.
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24 Interviewees did not agree that compensation would impair their judgment regarding a trial's risks and
25 benefits. They also argued that adults are capable of making a judgment of the risks involved and
26 deciding independently what they are willing to undertake for a financial incentive. They also argued
27 that the higher the risk of a trial, the higher the compensation should be. A few women mentioned that
28 payment should not exceed compensation for travel costs and time, and should not be the only reason
29 for participation.
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35 *Yes, so I don't know if you now say that very poor people are forced to take part in some*
36 *studies. That is, I find, actually not quite a correct statement, because I think there is no one*
37 *who tells people you have to participate in this study. So I think that's always an individual*
38 *decision that everyone can decide for himself whether he wants to join a study or not (non-*
39 *incentive, waiting list group).*
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44 *Hmm. But I think that ... it would be difficult to find participants at all. ... I think that's always*
45 *the problem ... and, uh -...- yes. It's just always the question of how necessary it is ... to do this*
46 *study. ... So I'm thinking: you must then weigh up, is it now really ... worth it, that it might also*
47 *save people from harm, ... or uh, does it not have to be. But I think that since the*
48 *pharmaceutical industry also puts a lot of money in such studies, they could also do it [offer*
49 *financial compensation] (incentive, intervention group).*
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53 54 55 **DISCUSSION**

56 In this study, we show that the characteristics of the AKUD trial – including offering a desired-for
57 intervention, the condition in question, and providing a financial incentive – were deciding factors for
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3 trial participation. It was particularly significant that the trial dealt with a condition of importance to
4 the women – menstrual pain interfered considerably with their lives on a monthly basis – and for
5 which the medical system did not provide them with sufficient or effective treatment options. AKUD
6 provided a potential solution to their problem, as interviewees believed that trial participation was an
7 important way to change existing medical options.
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12 Our findings are in line with other studies that have reported that individuals are motivated to
13 participate in research for a complexity of reasons. Benefits for self and others were the most
14 commonly mentioned reasons,^{16 19} as well as making a contribution to research – which was linked to
15 women’s own difficulties in finding a solution to their pain and the perception that others might be
16 faced with the same problem –, seeking pain relief, trying a different solution and monetary
17 remuneration. Unlike in the study of Wasan et al.,¹⁹ however, which showed that good experience with
18 new treatments and with prescribing physicians was a key driver for research participation, among our
19 interviewees the women were motivated by a dissatisfaction with their health care providers’
20 solutions.
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27 Townsend and Cox found that people participate in health research in order to access treatment and
28 health services otherwise unavailable.¹⁶ This was also a motivation cited in our study. But while all
29 interviewees participated for personal benefit, for some it was a clear secondary aim to increase the
30 available treatment options for menstrual pain within routine medical care. The women had a clear
31 understanding that evidence derived from clinical trials is a necessary precursor to introducing
32 treatments in medical care, and they wanted to make their contribution to scientific development and
33 improve the medical system.
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39 Payment of research participants can be a motivator for trial participation, although it also raises
40 concerns. In our study, the small financial compensation of €30 may have accelerated recruitment. But
41 while the majority of participants appreciated the financial compensation, independently of whether
42 they had been recruited before or after compensation was introduced, it was not given by any
43 interviewees as a main reason for participation, though some mentioned it as a subsidiary motivation.¹⁹
44 Furthermore, the narratives of our research participants indicate that the risks and benefits of entering
45 AKUD were actively weighed up when deciding to participate, and that financial compensation was
46 an additional determinant in this evaluation. Interviewees also did not agree that compensation impairs
47 the judgment of risk, which supports the argumentation of Dunn and colleagues who mentioned that
48 any kind of compensation is one of several factors in the research participation decision.²⁶ Our
49 findings do contrast with those of Russell and colleagues,¹⁴ however, who found that payment of
50 research participants was not generally accepted, except in case of recruitment problems and payment
51 for expenses and travel costs.
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In some instances and under certain circumstances, clinical trial participation can transform individual suffering into a meaningful experience.²⁷ While such a transformation cannot be deduced from our interviewees' narratives, our findings nevertheless show participants as active rather than passive research subjects with their own agenda about why the clinical trial could be important. This relates to Morris and Balmer's description of the active engagement of volunteers in research.²⁸

Regarding the limitations of our study, it should be mentioned that our study sample was highly educated, and one-third of interviewees mentioned having a medical background. Furthermore, women who are satisfied with the solutions offered by the medical system for menstrual pain, mainly painkillers and oral contraceptives, had no reason to participate in the AKUD trial. This sampling bias is reflected in the small number of women (n=7; 28%) in our sample taking oral contraceptives, compared to women aged 18-29 years in the general population, of whom 72% take oral contraceptives.²⁹ The presented results must therefore be interpreted with this in mind. Another limitation of the study is that we conducted interviews only with women who had consented to participate in the AKUD trial and not with those with menstruation problems who refused to participate. Finally, the women in the incentive group were older in comparison to those in the non-incentive group, which was the result of the increase in the age limit during the recruitment process.

Our results contribute to the ongoing discussion of whether financial compensation of research participants creates a risk of undue inducement. The women's narratives support the view that potential participants are able to assess risks and benefits and make legitimately voluntary choices. Women also acknowledged that while financial compensation might impact their decision-making process, it does not affect their judgment about risk. Finally, we further argue that the importance of clinical trials providing new treatments that could change medical practice might be an overlooked motivation for trial participation, and could be used as an argument in future recruitment strategies.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Conceived and designed the study: CMW, CH, SB

Data analysis and interpretation: SB, CH, CMW

Wrote the first draft of the manuscript: SB

All authors discussed the results, commented on the manuscript, and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIALS

Due to data protection restriction additional data are not available.

ACKNOWLEDGEMENTS

We thank the women for their participation and openness.

REFERENCES

1. Bower P, Brueton V, Gamble C, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014;15:399.
2. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;7:9.
3. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013;14:166.
4. Caldwell PH, Hamilton S, Tan A, et al. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med* 2010;7(11):e1000368.
5. Treweek S, Mitchell E, Pitkethly M, et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010(1):MR000013.
6. Campbell MK, Snowdon C, Francis D, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technol Assess* 2007;11(48):iii, ix-105.
7. Edwards P, Cooper R, Roberts I, et al. Meta-analysis of randomised trials of monetary incentives and response to mailed questionnaires. *J Epidemiol Community Health* 2005;59(11):987-99.
8. VanderWalde A, Kurzban S. Paying human subjects in research: where are we, how did we get here, and now what? *J Law Med Ethics* 2011;39(3):543-58.
9. Fry CL, Ritter A, Baldwin S, et al. Paying research participants: a study of current practices in Australia. *J Med Ethics* 2005;31(9):542-7.
10. Roche E, King R, Mohan HM, et al. Payment of research participants: current practice and policies of Irish research ethics committees. *J Med Ethics* 2013;39(9):591-3.
11. Cryder CE, John London A, Volpp KG, et al. Informative inducement: study payment as a signal of risk. *Soc Sci Med* 2010;70(3):455-64.
12. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. *J Med Ethics* 2004;30(3):293-8.
13. Wong JC, Bernstein M. Payment of research subjects for more than minimal risk trials is unethical. *Am J Med Sci* 2011;342(4):294-6.
14. Russell ML, Moralejo DG, Burgess ED. Paying research subjects: participants' perspectives. *J Med Ethics* 2000;26(2):126-30.
15. Toye F, Seers K, Barker K. A meta-ethnography of patients' experiences of chronic pelvic pain: struggling to construct chronic pelvic pain as 'real'. *J Adv Nurs* 2014;70(12):2713-27.
16. Townsend A, Cox SM. Accessing health services through the back door: a qualitative interview study investigating reasons why people participate in health research in Canada. *BMC Med Ethics* 2013;14:40.
17. Locock L, Smith L. Personal benefit, or benefiting others? Deciding whether to take part in clinical trials. *Clin Trials* 2011;8(1):85-93.
18. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials* 2010;11:31.

19. Wasan AD, Taubenberger SP, Robinson WM. Reasons for participation in pain research: can they indicate a lack of informed consent? *Pain Med* 2009;10(1):111-9.
20. Blodt S, Schutzler L, Huang W, et al. Effectiveness of additional self-care acupressure for women with menstrual pain compared to usual care alone: using stakeholder engagement to design a pragmatic randomized trial and study protocol. *Trials* 2013;14:99.
21. Ritchie M, L JK, Moss J, et al. Exploring attitudes towards a randomised controlled trial of venous access devices - a nested pre-trial qualitative study. *J Vasc Access* 2015;0(0):0.
22. Beckett K, Goodenough T, Deave T, et al. Implementing an Injury Prevention Briefing to aid delivery of key fire safety messages in UK children's centres: qualitative study nested within a multi-centre randomised controlled trial. *BMC Public Health* 2014;14:1256.
23. Holmberg C, Rappenecker J, Karner JJ, et al. The perspectives of older women with chronic neck pain on perceived effects of qigong and exercise therapy on aging: a qualitative interview study. *Clin Interv Aging* 2014;9:403-10.
24. Miles MB, Huberman M. Qualitative data analysis. An expand sourcebook. . London:: Sage Publication 1994.
25. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res* 2005;15(9):1277-88.
26. Dunn LB, Gordon NE. Improving informed consent and enhancing recruitment for research by understanding economic behavior. *JAMA* 2005;293(5):609-12.
27. Holmberg C, Whitehouse K, Daly M, et al. Gaining control over breast cancer risk: Transforming vulnerability, uncertainty, and the future through clinical trial participation - a qualitative study. *Sociol Health Illn* 2015.
28. Morris N, Balmer B. Volunteer human subjects' understandings of their participation in a biomedical research experiment. *Soc Sci Med* 2006;62(4):998-1008.
29. Bundeszentrale für gesundheitliche Aufklärung. Verhütungsverhalten Erwachsener. Köln, 2011.

BMJ Open

Women's reasons for participation in a clinical trial for menstrual pain – a qualitative study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012592.R1
Article Type:	Research
Date Submitted by the Author:	17-Aug-2016
Complete List of Authors:	Blödt, Susanne; Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin Witt, Claudia; 1Charité University Medical Center, Institute for Social Medicine, Epidemiology and Health Economics; UniversitätsSpital Zurich, Institute for Complementary and Integrative Medicine Holmberg, Christine; Charité Universitätsmedizin Berlin, Berlin School of Public Health
Primary Subject Heading:	Qualitative research
Secondary Subject Heading:	Complementary medicine
Keywords:	clinical trial participation, motivation, financial compensation, treatment options, dysmenorrhea

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Manuscripts

Women's reasons for participation in a clinical trial for menstrual pain – a qualitative study**Running title:** Women's reasons for trial participationSusanne Blödt¹, Claudia M Witt^{1,2}, Christine Holmberg³¹ Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin
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Keywords: clinical trial participation, motivation, financial compensation, treatment options,
dysmenorrhea**Word count:** abstract: 251; text: 4522

ABSTRACT

Objectives: The aim of the study was to explore women's motivations for participating in a clinical trial and to evaluate how financial compensation impacts women's explanations for participation.

Design, setting, and participants: Semi-structured interviews were conducted face-to face or by telephone with 25 out of 220 women who participated in a pragmatic randomized trial for app-administered self-care acupressure for dysmenorrhea (AKUD). Of these 25 women, 10 had entered AKUD knowing they would receive a financial compensation of €30. A purposive sampling strategy was used.

Results: Women had a long history of seeking help from their physicians and were unsatisfied with the options available, namely painkillers and oral contraceptives. While all interviewees were open to painkillers, they were uneasy about taking them on a monthly basis. The AKUD trial offered the possibility to find an alternative solution. A second reason for participation was the desire to add a new treatment to routine medical care, for which the interviewees considered randomized trials a prerequisite. The financial incentive was a subsidiary motivation in the interviewees' narratives.

Conclusion: Our results contribute to the ongoing discussion of the impact of financial compensation on research participants' assessment of risk. The interviewed women considered all research subjects able to make their own choices regarding trial participation, even in the face of financial compensation or payment of study participants. Furthermore, the importance of clinical trials providing new treatments that could change medical practice might be an overlooked reason for trial participation, and could be used in future recruitment strategies.

Strengths and limitations of the study

- The special setting of our study that included women who had entered the clinical trial both knowing and not knowing that they would receive a financial compensation of €30 allowed us to focus on the role of financial compensation in the decision-making processes of women when deciding on trial participation.
- The study contributes to understand how altruistic and personal reasons influence trial participation.
- Sampling bias might have occurred because our sample was predominantly highly educated, including many with a medical background.
- Generalizability of our results is confined to women unsatisfied with the solutions for menstrual pain offered within the health system.

INTRODUCTION

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3 Randomized clinical trials are seen as the gold standard in clinical research, yet their success depends
4 on the willingness of people to volunteer. Poor recruitment for clinical studies impacts statistical
5 power, internal and external validity, and can cause financial and practical restrictions.¹ Recruitment
6 problems are a common obstacle in clinical studies^{2 3} and numerous strategies have been identified to
7 improve recruitment, including programs to increase potential participants' awareness of a health
8 problem and its possible impact on them,⁴ making telephone contact with potential participants, and
9 using opt-out rather than opt-in procedures.⁵ Campbell et al. found that certain factors proved
10 successful in recruitment, including having a dedicated trial manager, it being a cancer drug trial, and
11 having interventions only available within the trial.⁶ Thus both trial characteristics and communication
12 strategies with potential participants are of importance for recruitment.
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20 The payment of research participants has also been shown to increase participation.⁷ Such a strategy is
21 controversial, however, as it may influence individuals' informed decision-making.⁵ In particular, it is
22 argued that payment may unduly influence socio-economically disadvantaged populations,⁸ and could
23 jeopardize informed consent and participants' autonomous ability to properly assess risks and
24 benefits.^{9 10} Indeed, studies have shown that higher compensation increases willingness to participate,
25 and that participants will assume higher risks when compensation is high.^{11 12} It has been argued that
26 whether it is ethical to pay research participants depends on the purpose of payment.⁸ Ethical concerns
27 do not generally affect studies with minimal risk of harm¹³ or those that reimburse only for time and
28 travel expenses,⁹ but do arise when payments exceed a certain threshold and/or compensate for
29 potential risk.
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37 There exists a range of studies from the USA investigating the participation of healthy volunteers in
38 phase 1 clinical trials.¹⁴⁻¹⁷ Such trials investigate a treatment in humans for the first time to test the
39 safety of a drug, and are thus precarious in several ways and pose particular ethical problems. For
40 instance, the risk of participation is unknown, and they require healthy volunteers that will be very
41 closely monitored and must invest a large amount of their time. For this, participants receive payment.
42 Often, participants in phase 1 studies include people in precarious financial situations, who may be
43 serial study participants.^{14 15 18}
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50 To our knowledge, only one study to date has looked at research subjects' perspectives on financial
51 compensation in phase 3 clinical trials – which assess the effectiveness of a new intervention and its
52 value in clinical practice – with mixed results.¹⁹ Some of the unpaid participants argued that
53 compensation is a valid recognition of participants; others clearly disagreed with the idea of paid
54 participation, arguing that it is a moral duty. Altruism and the wish to benefit others and oneself have
55 been identified as major reasons for participating in phase 3 clinical trials,²⁰⁻²⁴ though given the
56 evidence that communication strategies and trial characteristics might also be important motivations,
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3 the question arises of what altruism, moral duty, and benefit to others actually imply. Indeed, it
4 remains unclear how financial compensation actually influences participants' willingness to enroll in
5 research, and what other factors also play a role.
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9 *Trial for acupressure against menstrual pain (AKUD)*

10 The randomized pragmatic trial AKUD²⁵ was set up to assess the effectiveness of self-acupressure
11 supported by a smart phone app (intervention), compared to usual care (control group), for 220 women
12 with menstrual pain (trial registered at clinicaltrials.gov under NCT01582724). All women received
13 the AKUD app, which provided questionnaires, diaries, and for the women in the intervention group
14 guidance on self-acupressure. The trial ran from December 2012 to April 2015. Women were recruited
15 in Berlin, Germany from December 2012 to August 2014 through posters and flyers at university
16 campuses in Berlin, the intranet platforms of Charité - Universitätsmedizin Berlin, and advertisements
17 on two Berlin subway lines for 5 months.
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20 Women in the intervention group were asked to apply acupressure 5 days before the start of
21 menstruation (1-2 times a day, 6 minutes per session) and on the days of pain (up to 6 times a day).
22 Upon completion of the study, the acupressure features were activated on the app for the women in the
23 control group and those interested could receive a personal introduction at the Institute for Social
24 Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin.
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26

27 To increase participation rates, the study group decided after eight months to introduce a financial
28 compensation of €30 and to change the upper age limit for participants from 25 to 34 years. We
29 announced the introduction of the financial compensation, including the amount, on the
30 advertisements for the AKUD study. On the more detailed AKUD information leaflet, we added that
31 after successful study participation, participants would receive a compensation of €30. Trial
32 participants that had completed all questionnaires were informed by email that they could collect their
33 €30 at the Institute (later on in the trial, the money was transferred to participants' bank accounts).
34 Women who participated in AKUD before the financial compensation was introduced received the
35 information about the compensation at the latest upon completion of the study.
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38 As a result of these changes (financial compensation, change of age range) the monthly recruitment
39 figures for AKUD almost doubled (mean n=13.4 per month after the changes compared to mean n=7
40 per month before). Women who were interested in participating in the study were invited to the
41 Institute once for a screening and baseline visit (duration approximately 30-60 minutes). All other
42 quantitative data were collected through the app with a time requirement of 5-10 minutes per cycle.
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3 The aim of this qualitative study was to analyze women's motivations for participating in the trial,
4 including whether the small financial compensation had an impact, and to assess women's general
5 views on financial incentives for research participation.
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8 9 **METHODS**

10 **Design**

11 This qualitative study was nested in the AKUD trial,²⁵ and was conducted by the Institute for Social
12 Medicine, Epidemiology and Health Economics at the Charité - Universitätsmedizin Berlin.
13

14 Qualitative, semi-structured interviews were conducted with trial participants after they had completed
15 all questionnaires for the AKUD trial, in order to avoid influencing the results of AKUD.
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17 The study was approved by the Charité - Universitätsmedizin Berlin Ethics Committee (28.08.2013 -
18 EA1/027/12).
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22 **Sampling and recruitment**

23 Based on experience from other qualitative studies nested in randomized clinical trials, a sample size
24 of 20-30 participants was aimed for.²⁶⁻²⁸ Recruitment for the qualitative study took place between
25 September 2013 and January 2015, with the selected participants invited for an interview by mail or
26 phone. Up to March 2014, 26 women in the intervention and 23 women in the control group were
27 informed about the qualitative study; this led to 21 interviews up to March 2014. The sampling
28 strategy was purposeful, with the sample selected based on whether the women had been recruited to
29 AKUD before or after financial compensation had been introduced. The aim was to interview more
30 women (a minimum of 15) who had been recruited prior to the introduction of the incentive, as we
31 assumed that their reasons would be more diverse and would differ from those who participated after
32 the introduction of the incentive, for whom we assumed the financial incentive had played an
33 important role.
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42 In addition to the two groups 'non-incentive' and 'incentive', for our sampling strategy we further
43 distinguished the women according to whether they had been randomized to the intervention or to the
44 waiting list (control group). We aimed for an equal distribution across the intervention and control
45 groups for the interview sample.
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49 Participants were invited to the qualitative study until we had achieved 21 interview participants.
50 Those who were not interested in conducting an interview (approximately 24 women) mentioned time
51 constraints and no interest as reasons. We then analyzed the materials and resumed recruitment in
52 March 2015, adding another 4 interviewees to the sample to verify the findings of the analysis and
53 ensure data saturation.
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Data collection

The first 21 interviews took place at the Institute, the final four interviews were conducted by phone. All interviews were conducted only after written informed consent had been provided by interviewees.

The interviews were semi-structured according to an interview guide that had been developed based on the research question, existing literature, and discussion within the study team (Table 1). Additionally, socio-demographic information, pain intensity, and medication use were collected for all interviewees.

All interviews were conducted one-to-one by SB. All authors are experienced qualitative researchers. SB received training in qualitative interviewing from CH and initial interviews were discussed by the research team and in a qualitative research group at the Charité with regards to interview techniques and improvements in the interview guide. SB was responsible for the overall organization of the AKUD trial but had no contact with study participants and therefore did not know the interviewees beforehand.

Analysis

After each interview, the interviewer wrote an interview summary form²⁹ that included interpersonal aspects of the interviews as well as brief summaries for each research question based on interviewees' statements. These interview summary forms were included in the analysis to account for the relationship between interviewer and interviewee in data analysis.²⁹ The interviews were digitally recorded and transcribed verbatim. Transcripts were pseudonymized by changing the women's names. Transcripts were uploaded into the software program MAXQDA (version 11 for Mac) and a thematic analysis of the transcripts was conducted.³⁰

All interview material was coded by SB. The first round of coding was done based on the interview guide. After this initial coding process to structure the data, each coded segment was analyzed for present themes and coded accordingly. These two rounds of coding were conducted by SB for the first five interviews. The resulting themes and the coding tree were discussed by SB and CH and in a qualitative research group at the Charité to ensure intersubjectivity and grounding in the analysis. The coding process then continued for the first 21 interviews. In this process, major themes emerged that were discussed by the research team. All analysis steps were documented in written memos. After 21 interviews, analysis was considered complete as the same important themes continued to occur. Results were presented and discussed by the research team. To verify the findings of the analysis, four additional interviews were conducted, which presented the same themes and thus data collection was terminated.

RESULTS

Sample

Twenty-five women were interviewed (duration 10-50 minutes, mean 27 min), of which 15 had been recruited to AKUD without financial incentive and ten with financial incentive (Table 2). The mean age of the women in the non-incentive group was 22.7 years (range 21–25) and in the incentive group 26.4 years (range 24–33). The interviewees were mostly highly educated and one-third mentioned having a medical background (e.g. medical student or working at the Charité - Universitätsmedizin Berlin). The majority (n=19) of interviewees took painkillers for their menstrual pain, with ibuprofen, aspirin, and paracetamol being the most common.

Thematic findings

Analysis of the interviews showed that in order to understand women's participation in the AKUD trial, an understanding of their prior situation was important; namely, they all routinely experienced a significant impact of menstrual pain on their lives. All of the women had a history of searching for an appropriate solution and were unsatisfied with the limited options offered to them by their health care providers, namely painkillers or the contraceptive pill. While all interviewees were open to painkillers, they were uneasy about taking them on a monthly basis. Interviewees had an understanding that randomized clinical trials are a necessary prerequisite to introducing a new treatment option into medical care. The financial compensation received was seen as a nice and appropriate bonus to their AKUD participation. Below we describe the abovementioned themes in detail. While analysis was conducted separately for the incentive and non-incentive groups, results were similar. The findings are thus presented jointly, except with regard to financial compensation.

Women's situation prior to trial participation

All women described how menstruation pain impacted their daily lives and disturbed their normal routines. For some, taking analgesics or the oral contraceptive pill alleviated the pain enough to allow their activities to continue. Others discussed how the pain affected everything – their social life, education, work – and was all-encompassing while it endured; some had to stay in bed and avoid all activities outside the house. Many interviewees described increased pain in stress situations and thus actively tried to reduce stress during menstruation. Such coping strategies became problematic when menstruation coincided with appointments that could not be postponed, while cancellation of appointments and work absences caused additional emotional stress for some women. Sometimes, the pain also ruined key planned events.

Yes, right, (...) menstrual pain is just stupid, it messes up everything. It always comes when you have a birthday, or Christmas or when something is ... nice actually, and then it's always so

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3 *annoying when ... you just lie in bed the whole time, or have to take a whole lot of painkillers*
4 *(Berta, non-incentive, intervention group).*
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8 All interviewed women except for three regularly took analgesics to reduce their regular menstrual
9 pain. However, all continued to search for more satisfying care. For example, of those who did not
10 take analgesics at all, two dealt with their pain by lying down with a hot water bottle, while the third
11 took contraceptive pills specifically to reduce her menstrual pain. For some interviewees, although
12 they took analgesics and oral contraceptives, these medications were not effective in reducing their
13 pain or they had not tolerated the medication (n=4 non-incentive; n=4 incentive).
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18 None of the interviewees were against medication in general, though they did perceive it critically due
19 to the potential side effects. They also did not generally think that alternative medicine is better than
20 usual medicine. Nevertheless, they shared a critical view on analgesics as a regular solution for
21 menstrual pain. The regularity and continuity of menstruation and the related pain, as mentioned by
22 five women (n=2 non-incentive; n=3 incentive), made it difficult to accept analgesia as an appropriate
23 solution.
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29 *So for me perhaps already the primary decisive reason was ... because I thought maybe it helps*
30 *somehow. And because it always bothered me that I have to take so many painkillers. If once a*
31 *month you always have to take so many painkillers ... actually I do not like the feeling (Viola,*
32 *incentive, intervention group).*
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36 Many of the participants had sought alternatives to analgesics – including household remedies such as
37 hot water bottles and tea – but with limited success. Some participants had tried, with mostly minimal
38 effect, acupuncture, herbs, homeopathy, dancing/movement, and gymnastics. Such experiences left the
39 women feeling alone with their complaints and disillusioned with the medical system that had too few
40 options for treating menstrual pain.
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44 45 **Deciding on the AKUD trial**

46 *Hope for relief with no added risk*

47 The AKUD trial was seen as a possible solution for their pain. The main reason for all interviewees for
48 participation was to find a new or additional means to deal with their monthly ordeal.
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53 *So it's as I said. I'm sick once a month and I find that quite a limitation given the fact that it's*
54 *[menstrual pain] not a disease. ... And I just hoped that something could help. That I could just*
55 *... cope with my everyday life. ... Because up to now there has been no solution (Zara,*
56 *incentive, intervention group).*
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4 For many interviewees it was important that the AKUD trial offered a non-drug therapy as a treatment
5 option. As a reason for participation, the interviewees stressed the fact that they considered
6 acupressure to be natural and thus could do no harm, more than they cited the potential effectiveness
7 that acupuncture may have. Therefore most of them had decided upon participation spontaneously
8 while reading about the trial on posters at locations such as the Charité or on official advertisement
9 bulletins in the subway system. They did not talk to friends, family, or physicians before making the
10 decision. Questions they may have had such as time commitment were asked when they contacted the
11 AKUD study center.
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17 *Adding a treatment option to medical care*

18 In addition to finding relief for their own monthly pain, some interviewees clearly indicated that their
19 participation could benefit other women, as a positive evaluation of acupressure would lead to more
20 treatment options that physicians could offer patients. Such ideas were coupled with their belief that
21 menstrual pain and dissatisfaction with current therapeutic options are an experience shared by many.
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27 Women considered their study participation an important part of building evidence for medical
28 practice. Because they assumed that the trial results would help change medical practice, they were
29 also open to the procedure of randomization as a means to obtain valuable scientific evidence.
30 Interviewees likewise emphasized the importance of informing gynecologists if the results of the study
31 were positive, in the hope of reaching as many women as possible.
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36 *Exactly, I also wish that it, acupressure, somehow turns out to be a big success, and that it*
37 *might be a real option. ... So for me the study proved really meaningful and you could say ...*
38 *okay, women have ... such and such a percentage somehow to thereby have an improvement or*
39 *so. ... And then you could, maybe you can actually publish that and can say, okay ... try this ...*
40 *(Mia, non-incentive, control group).*
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45 *App as a motivational technology*

46 Interviewees found the app useful and convenient, however none considered it a reason for
47 participation.
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51 *SB: And the app? Was that a motivation to take part in the study?*

52 *Dora: Um, well a motivation, I don't know, but I, it was very convenient in any case (non-*
53 *incentive, control group).*
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58 **Financial benefit**

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3 Although financial gain could not have been a motivation for participation for the 15 women in the
4 non-incentive group, all of the women in both groups expressed gratitude for the financial
5 compensation. The majority agreed that financial compensation to cover transportation and time
6 expenditure is appropriate for the efforts of trial participation. Only two women in the non-incentive
7 group argued that the potential personal benefit outweighed any time expenditure and found financial
8 compensation unnecessary.
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13 *Yes exactly. I see no reason, actually, no reason, uh, that you pay us for it [participation]. ...*
14 *Because ... uh, the people who participate gladly take the time for it and ... are not forced into*
15 *it, so ... I don't know. For me it goes without saying that when there is actually no money, that it*
16 *is not about money. Because, uh, you give us something. So we, we give our time, but we usually*
17 *get a positive result, so ... (Olga, non-incentive, control group).*
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23 Some women in the incentive group did argue that financial compensation had been a deciding factor
24 for participation (n=2). The majority of interviewees were students or in vocational training, and they
25 mentioned the importance of a small subsidy to cover daily expenses.
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29 *Thea: Um ... on the other hand, even if, if it's not much money, it's just still the thirty Euros that*
30 *we as trainees, we're just ... always at the limit anyway. Yes, still not a lot of money and then*
31 *doing it also for thirty Euros is also ... a trifle.*
32

33 *SB: Hmm, hmm. That was, so that was also something extra, it was an added incentive.*

34 *Thea: Yes (incentive, intervention group).*
35
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38 Overall, interviewees believed that clinical trials are necessary to improve medical practice. Thus
39 payment to incentivize recruitment is also necessary, since without it medical progress could be
40 endangered.
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44 Interviewees did not agree that compensation would impair their judgment regarding a trial's risks and
45 benefits. They also argued that adults are capable of making a judgment of the risks involved and
46 deciding independently what they are willing to undertake for a financial incentive. They also argued
47 that the higher the risk of a trial, the higher the compensation should be. A few women mentioned that
48 payment should not exceed compensation for travel costs and time, and should not be the only reason
49 for participation.
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54 *Yes, so I don't know if one can say that very poor people are forced to take part in some studies.*
55 *That is, actually I find this not quite a correct statement, because I think there is no one who*
56 *tells people you have to participate in this study. So I think it's always an individual decision*
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3 *that everyone can decide for himself whether he wants to join a study or not (non-incentive,*
4 *control group).*
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8 *Hmm. But I think that ... it would be difficult to find participants at all. ... I think that's always*
9 *the problem It's just always the question of how necessary it is ... to do this study. ... So I'm*
10 *thinking: you must then weigh up, is it now really ... worth it, that it might also save people from*
11 *harm, ... or uh, does it not have to be? But I think that since the pharmaceutical industry also*
12 *puts a lot of money into such studies, they could also do it [offer financial compensation]*
13 *(Viola, incentive, intervention group).*
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17 18 **DISCUSSION**

19 In this study, we show that the alignment of a range of factors and the characteristics of AKUD –
20 offering a desired-for intervention, dealing with menstrual pain, and that the intervention was viewed
21 as harmless – were decisive for trial participation. In particular, the trial addressed a condition of
22 importance to the women – that is, a monthly ordeal for which the medical system provides treatment
23 options with which the women were uneasy, and for which they hoped to add another therapeutic
24 option through their trial participation. It is also interesting that contrary to other studies that have
25 shown that trust in physicians and good experience with the health care system may be reasons for
26 volunteering in research,^{24 31} the women in our study were dissatisfied with the medical care for their
27 menstrual pain, which led them to participate in AKUD.
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30 One may argue that, similar to other studies,^{21 24 31} the women in our study participated in AKUD to
31 achieve benefits both for themselves and for others. The women articulated personal benefits from
32 participation as a motivation, but were clear that they also saw benefits of trial participation beyond
33 themselves. The women had a clear expectation that if the trial results were positive their participation
34 would mean that women with menstrual pain would receive the new treatment option through their
35 physicians. Thus they had a clear understanding that medical practice is based on clinical trials and
36 they expected clinical trial results to be translated directly into medical practice. Unlike some other
37 studies^{17 19}, none raised ideas of moral duty for participation.
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40 As McCann has argued, for actual participation personal benefit is necessary, even though benefit for
41 others is a reason to consider participation. This she calls “conditional altruism.”²³ In this context, one
42 may discuss financial compensation. Paying participants clearly increases trial participation.^{7 15-17}
43 However, it is controversial as it may impede the idea of volunteerism^{14 16}, and also stands in contrast
44 to the idea of participation as a moral duty¹⁹. The few studies conducted on research subjects' views
45 on financial compensation have mostly focused on healthy volunteers in phase 1 trials¹⁴⁻¹⁷. Although
46 the women in our trial considered themselves healthy, their situation was quite different from phase 1
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3 volunteers. Healthy volunteers in general are exposed to risk and discomfort, receiving in exchange
4 money or access to health care otherwise unavailable.^{14 17} Contrary to phase 1 trials, AKUD was a low
5 risk trial offering an unknown but promising therapeutic option for a condition with a high impact on
6 quality of life. Some have argued that in phase 1 trials, risks are downplayed and financial
7 compensation may affect autonomy and informed consent.^{14 16} Indeed, women in our study argued that
8 while compensation for trial participation is appropriate, it should not be a wage. However,
9 interviewees were clear that research participants are autonomous individuals with the ability to make
10 informed decisions and to assess the potential risks and benefits for themselves, also when there is
11 financial compensation.

12
13 Furthermore, while some respondents mentioned that financial compensation was important for them
14 in deciding upon trial participation, it was not given by any as the deciding factor. Taking into
15 consideration the suggestion of other authors that financial motivation may not initially be mentioned
16 because it is not perceived as socially acceptable,³² the fact that the women in the incentive group were
17 older compared to those in the non-incentive group nevertheless clearly suggests that the recruitment
18 rate for AKUD accelerated not only due to the increase in the age limit.

19
20 Another point that may have been of importance in the AKUD trial was the condition in question,
21 namely menstrual pain. Menstrual pain is difficult to categorize in the usual terms of “sick” and
22 “healthy.” Menstruation is considered “natural” and “normal,”³³ but at the same time some women
23 experience severe menstrual pain or other unpleasant symptoms. For instance, women in our study
24 reported the need to limit their activities and reduce stress during menstruation, which impacted their
25 daily lives and could lead to occupational impairment.³⁴⁻³⁶ For this ambivalent state, there exist no
26 culturally recognized strategies for menstruating women outside of biomedicine, and the existing
27 biomedical options were, for the women in our study, either ineffective or undesirable. This
28 ambivalent state³⁷ may be an important reason why self-care approaches, such as the one tested in
29 AKUD, may be seen as a better option than painkillers, as they are also considered “natural.”³⁴

30
31 Regarding the limitations of our study, it should be mentioned that our study sample was highly
32 educated, and one-third of interviewees mentioned having a medical background. Furthermore,
33 women who are satisfied with the solutions offered by the medical system for menstrual pain, mainly
34 painkillers and oral contraceptives, had no reason to participate in the AKUD trial. This sampling bias
35 is reflected in the small number of women (n=7; 28%) in our sample taking oral contraceptives,
36 compared to women aged 18-29 years in the general population, of whom 72% take oral
37 contraceptives.³⁸ The presented results must therefore be interpreted with this in mind.

Our results contribute to the ongoing discussion of whether financial compensation of research participants creates a risk of undue inducement. The women in our study considered themselves and others capable of adequately assessing risks and benefits and thus of making legitimately independent and voluntary choices. The women were clear that while financial compensation might have an impact on their decision-making process, it would not affect their judgment about risk. Finally, we suggest that the importance of clinical trials providing new treatments that could change medical practice might be an overlooked motivation for trial participation that needs to be addressed in future recruitment strategies.

Implication for practice

Our study findings indicate that recruitment strategies should address the issue of the translation of study results into clinical practice and the potentials and pitfalls for shaping clinical practice through trial participation. A further point to address might be dissatisfaction with available treatment options, especially in case of “normal” conditions that have an impact on quality of life and for which biomedical treatments may not be the first or preferred choice for those affected, although they might nevertheless ask their medical providers for help. Opening up medical care for integrative approaches for such conditions should be considered.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Conception and design of the study: CMW, CH, SB

Data analysis and interpretation: SB, CH, CMW

First draft of the manuscript written by: SB

All authors discussed the results, commented on the manuscript, and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIALS

Due to data protection restrictions, additional data are not available.

ACKNOWLEDGEMENTS

We thank the women for their participation and openness.

Table 1: Interview guide

<p>You have participated in the AKUD trial, which investigated the effectiveness of acupressure against menstrual pain.</p> <p>Motivation for participation What reasons did you have to participate? Was the app a reason to participate? Was the €30 a reason to participate?</p> <p>Decision-making How did you decide to participate? Where did you hear about the study? With whom, if anyone, have you discussed your study participation? Have you participated in other studies? If so, what was your experience? Do you have prior experience with acupressure or other complementary therapies? If so, what was your experience?</p> <p>Menstrual pain How have you dealt with menstrual pain prior to the AKUD study? How have you experienced menstrual pain in your daily life?</p> <p>Opinion incentive What is your view on payment of research participants?</p>

Table 2: Characteristics of the interviewees and the motivations for participation at baseline

	Recruitment without incentive <i>n=15</i>		Recruitment with incentive <i>n=10</i>	
	Intervention <i>n=4</i>	Control <i>n=11</i>	Intervention <i>n=9</i>	Control <i>n=1</i>
Mean age (M, SD)	23.3 ± 2.1	22.6 ± 2.0	26.6 ± 2.8	25
≥ 12 years of school education	3	11	9	1
Painkiller or hormonal contraceptive against menstruation pain	4	9	6	1
Mean pain intensity during last menstruation (NRS: Mean, SD)	5.0 ± 2.2	5.3 ± 1.7	5.8 ± 1.6	7.0
Worst pain during last menstruation (NRS: M, SD)	7.5 ± 1.0	7.0 ± 1.3	6.9 ± 0.9	8.0

* More than one answer was possible, financial compensation was not an answer option

REFERENCES

1. Bower P, Brueton V, Gamble C, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014;15:399.
2. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;7:9.
3. Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013;14:166.
4. Caldwell PH, Hamilton S, Tan A, et al. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS medicine* 2010;7(11):e1000368.
5. Treweek S, Mitchell E, Pitkethly M, et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010(1):MR000013.
6. Campbell MK, Snowdon C, Francis D, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health technology assessment (Winchester, England)* 2007;11(48):iii, ix-105.
7. Edwards P, Cooper R, Roberts I, et al. Meta-analysis of randomised trials of monetary incentives and response to mailed questionnaires. *Journal of epidemiology and community health* 2005;59(11):987-99.
8. VanderWalde A, Kurzban S. Paying human subjects in research: where are we, how did we get here, and now what? *J Law Med Ethics* 2011;39(3):543-58.
9. Fry CL, Ritter A, Baldwin S, et al. Paying research participants: a study of current practices in Australia. *Journal of medical ethics* 2005;31(9):542-7.
10. Roche E, King R, Mohan HM, et al. Payment of research participants: current practice and policies of Irish research ethics committees. *Journal of medical ethics* 2013;39(9):591-3.
11. Cryder CE, John London A, Volpp KG, et al. Informative inducement: study payment as a signal of risk. *Social science & medicine (1982)* 2010;70(3):455-64.
12. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. *Journal of medical ethics* 2004;30(3):293-8.
13. Wong JC, Bernstein M. Payment of research subjects for more than minimal risk trials is unethical. *The American journal of the medical sciences* 2011;342(4):294-6.
14. Abadie R. The professional guinea pig. Durham and London, 2010.
15. Monahan T, Fisher JA. I'm still a hustler': entrepreneurial responses to precarity by participants in phase I clinical trials. *Economy and Society* 2015;44(4):545-66.
16. Fisher JA. Feeding and Bleeding: The Institutional Banalization of Risk to Healthy Volunteers in Phase I Pharmaceutical Clinical Trials. *Sci Technol Human Values* 2015;40(2):199-226.
17. Stunkel L, Grady C. More than the money: a review of the literature examining healthy volunteer motivations. *Contemp Clin Trials* 2011;32(3):342-52.
18. Cooper M, Waldby C. Clinical Labor: Tissue Donors and Research Subjects in the Global Bioeconomy. Durham and London: Duke University Press, 2014.
19. Russell ML, Moralejo DG, Burgess ED. Paying research subjects: participants' perspectives. *Journal of medical ethics* 2000;26(2):126-30.

20. Toye F, Seers K, Barker K. A meta-ethnography of patients' experiences of chronic pelvic pain: struggling to construct chronic pelvic pain as 'real'. *Journal of advanced nursing* 2014;70(12):2713-27.
21. Townsend A, Cox SM. Accessing health services through the back door: a qualitative interview study investigating reasons why people participate in health research in Canada. *BMC medical ethics* 2013;14:40.
22. Locock L, Smith L. Personal benefit, or benefiting others? Deciding whether to take part in clinical trials. *Clinical trials (London, England)* 2011;8(1):85-93.
23. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials* 2010;11:31.
24. Wasan AD, Taubenberger SP, Robinson WM. Reasons for participation in pain research: can they indicate a lack of informed consent? *Pain Med* 2009;10(1):111-9.
25. Blodt S, Schutzler L, Huang W, et al. Effectiveness of additional self-care acupuncture for women with menstrual pain compared to usual care alone: using stakeholder engagement to design a pragmatic randomized trial and study protocol. *Trials* 2013;14:99.
26. Ritchie M, L JK, Moss J, et al. Exploring attitudes towards a randomised controlled trial of venous access devices - a nested pre-trial qualitative study. *J Vasc Access* 2015;0(0):0.
27. Beckett K, Goodenough T, Deave T, et al. Implementing an Injury Prevention Briefing to aid delivery of key fire safety messages in UK children's centres: qualitative study nested within a multi-centre randomised controlled trial. *BMC Public Health* 2014;14:1256.
28. Holmberg C, Rappenecker J, Karner JJ, et al. The perspectives of older women with chronic neck pain on perceived effects of qigong and exercise therapy on aging: a qualitative interview study. *Clin Interv Aging* 2014;9:403-10.
29. Miles MB, Huberman M. Qualitative data analysis. An expand sourcebook. . London:: Sage Publication 1994.
30. Braun V, Clarke V. Using thematic analysis in psychology *Qualitative Research in Psychology* 2006;3:2:77-101.
31. Shah JY, Phadtare A, Rajgor D, et al. What leads Indians to participate in clinical trials? A meta-analysis of qualitative studies. *PloS one* 2010;5(5):e10730.
32. Soule MCM, Beale EEB, Suarez LM, et al. Understanding motivations to participate in an observational research study: Why do patients enroll? *Soc Work Health Care* 2016;55(3):231-46.
33. Grace VM, MacBride-Stewart S. 'Women get this': gendered meanings of chronic pelvic pain. *Health (London)* 2007;11(1):47-67.
34. Santer M, Wyke S, Warner P. Women's management of menstrual symptoms: findings from a postal survey and qualitative interviews. *Social science & medicine (1982)* 2008;66(2):276-88.
35. Brantelid IE, Nilver H, Alehagen S. Menstruation during a lifespan: A qualitative study of women's experiences. *Health care for women international* 2014;35(6):600-16.
36. O'Flynn N, Britten N. Menorrhagia in general practice--disease or illness. *Social science & medicine (1982)* 2000;50(5):651-61.
37. Burbeck R, Willig C. The personal experience of dysmenorrhoea: an interpretative phenomenological analysis. *J Health Psychol* 2014;19(10):1334-44.

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- 38. Bundeszentrale für gesundheitliche Aufklärung. Verhütungsverhalten Erwachsener. Köln, 2011.

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Domain 1	
1. Interviewer	Page 6
2. Credentials	SB: Page 1
3. Occupation	Page 6: SB was responsible for the overall organization of the AKUD trial but had no contact with study participants and therefore did not know the interviewees beforehand.
4. Gender	Page 1: Author is listed
5. Experience and training	Page 6: All authors are experienced qualitative researchers. SB received training in qualitative interviewing from CH and initial interviews were discussed by the research team and in a qualitative research group at the Charité with regards to interview techniques and improvements in the interview guide.
Relationship with participants	
6. Relationship established prior the study commencement	Page 6: SB was responsible for the overall organization of the AKUD trial but had no contact with study participants and therefore did not know the interviewees beforehand.
7. Participant knowledge of the interviewer	Name, function, place of employment
8. Interviewer characteristics	Page 14: Only the topics in the interview guide (Table 1) were addressed
Domain 2: Study design	
Theoretical framework	
9. Methodological orientation & theory	Page 6: and a thematic analysis of the transcripts was conducted. ³⁰
Participant selection	
10. Sampling	Page 5: The sampling strategy was purposeful, with the sample selected based on whether the women had been recruited to AKUD before or after financial compensation had been introduced. The aim was to interview more women (a minimum of 15) who had been recruited prior to the introduction of the incentive, as we assumed that their reasons would be more diverse and would differ from those who participated after the introduction of the incentive, for whom we assumed the financial incentive had played an important role.
11. Method of approach	Page 5: Recruitment for the qualitative study took place between September 2013 and January 2015, with the selected participants invited for an interview by mail or phone.
12. Sample Size	Page 7: Twenty-five women were interviewed (duration 10-50 minutes), of which 15 had been recruited to AKUD without financial incentive and ten with financial incentive (Table 2).
13. Non participation	Page 5: Those who were not interested in conducting an interview (approximately 24 women) mentioned time constraints and no interest as reasons.

14. Setting of data collection	Page 6: The first 21 interviews took place at the Institute, the final four interviews were conducted by phone.
15. Presence of non-participants	Page 6: All interviews were conducted one-to-one by SB
16. Description of sample	Page 7: The mean age of the women in the non-incentive group was 22.7 years (range 21–25) and in the incentive group 26.4 years (range 24–33). The interviewees were mostly highly educated and one-third mentioned having a medical background (e.g. medical student or working at the Charité - Universitätsmedizin Berlin). The majority (n=19) of interviewees took painkillers for their menstrual pain, with ibuprofen, aspirin, and paracetamol being the most common. Page 14: Table 2
Data collection	
17. Interview guide	Page 6: The interviews were semi-structured according to an interview guide that had been developed based on the research question, existing literature, and discussion within the study team (Table 1).
18. Repeat interviews	No repeat interviews were recorded.
19. Audio/visual recording	Page 6: The interviews were digitally recorded and transcribed verbatim.
20. Field notes	Page 6: After each interview, the interviewer wrote an interview summary form ²⁵ that included interpersonal aspects of the interviews as well as brief summaries for each research question based on interviewees' statements
21. Duration	Page 7: Interviews lasted between 10 and 50 minutes, mean 27 minutes –
22. Data saturation	Page 6: After 21 interviews, analysis was considered complete as the same important themes continued to occur in the analysis. Results were presented and discussed by the research team. To verify the findings of the analysis, four additional interviews were conducted, which presented the same themes and thus data collection was terminated.
23. Transcripts returned	The transcripts were not returned.
Domain 3: analysis and findings	
Data analysis	
24. Number of data coders	Page 6: All interview material was coded by SB. The first round of coding was done based on the interview guide. After this initial coding process to structure the data, each coded segment was analyzed for present themes and coded accordingly. These two rounds of coding were conducted by SB for the first five interviews. The resulting themes and the coding tree were discussed by SB and CH and in a qualitative research group at the Charité to ensure intersubjectivity and grounding in the analysis.

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25. Description of coding tree	Page 6: The first round of coding was done based on the interview guide. After this initial coding process to structure the data, each coded segment was analyzed for present themes and coded accordingly. These two rounds of coding were conducted by SB for the first five interviews. The resulting themes and the coding tree were discussed by SB and CH and in a qualitative research group at the Charité to ensure intersubjectivity and grounding in the analysis. The coding process then continued for the first 21 interviews.
26. Derivation of themes	Page 6: The first round of coding was done based on the interview guide. After this initial coding process to structure the data, each coded segment was analyzed for present themes and coded accordingly. These two rounds of coding were conducted by SB for the first five interviews. The resulting themes and the coding tree were discussed by SB and CH and in a qualitative research group at the Charité to ensure intersubjectivity and grounding in the analysis.
27. Software	Page 6: Transcripts were uploaded into the software program MAXQDA (version 11 for Mac)
28. Participant checking	Participants did not provide feedback on the findings.
Reporting	
29. Quotations presented	Page 7-11: Quotations are identified by pseudonyms.
30. Data and findings consistent	Page 7-11. Data and findings are consistent.
31. Clarity of major themes	Major themes are clearly presented on page 7-11.
32. Clarity of minor themes	Minor themes are clearly presented on page 7-11.