Methodological Challenges and Solution Strategies During Implementation of a Midwife-led Multicentre Randomized-controlled Trial (RCT) in Maternity Hospitals

Sabine Striebich (sabine.striebich@medizin.uni-halle.de)
Martin Luther University Halle-Wittenberg
Elke Mattern
hsg Bochum - University of Applied Sciences
Theresa Oganowski
hsg Bochum - University of Applied Sciences
Rainhild Schäfers
hsg Bochum - University of Applied Sciences
Gertrud M. Ayerle
Martin Luther University Halle-Wittenberg

Research Article

Keywords: Randomized-controlled trials (RCT), ICH-GCP, methodically challenging, obstetricians

Posted Date: March 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-331325/v1

Abstract

Background:

RCTs with complex interventions are methodically challenging. Careful planning under everyday conditions in compliance with the relevant international quality standard (ICH-GCP guideline) is crucial. Specific challenges exist for RCTs conducted in delivery rooms due to various factors that cannot be planned beforehand, such as “peak hours” of births and a high work burden for midwives and obstetricians. Moreover, in Germany as well as in other countries, midwives and obstetricians have frequently little experience as investigators in clinical trials.

Methods:

The randomised controlled trial “BE-UP” tests the effectiveness of an alternative birthing room on the rate of vaginal births and woman-oriented outcomes. In the process of implementing the trial in 17 obstetrical units and in the endeavour to reach the calculated sample size of 3,800 women, the research team encountered a variety of unexpected challenges. The aim is to describe in greater detail the methodical and organisational challenges and to inform about the research team’s strategies to overcome them.

Results:

The results are presented in five sectors:

1) Selection of and support for cooperating hospitals: they are to be selected according to predefined criteria and strategies to offer continuous support in trial implementation must be mapped out.

2) Establishing a process of requesting informed consent: a quality-assured process to inform pregnant women early on must be feasible and effective.

3) Individual, digital real time randomization: besides instructing the maternity teams appropriate measures for technical failure must be provided.

4) The standardized birthing room: the complex intervention is to be implemented according to study protocol, yet adapted to the prevailing conditions in the delivery rooms.

5) GCP-compliant documentation: midwives and obstetricians is to be instructed in high quality data collection, supported by external monitoring throughout the trial.

Conclusion:

Since not all potential challenges can be anticipated in the planning of a trial, study teams need to be flexible and react promptly to any problems that threaten recruitment or the implementation of the complex intervention. Thought should be given to the perspectives of midwives and obstetricians as recruiters and how clinic-intern processes could be adapted to correspond with the trial’s requirements.

Background

Quality of RCTs

Randomized-controlled trials (RCT) are the gold standard in clinical research; they generate findings with the highest level of evidence for improving the quality of patients' care. RCTs are methodically complex and costly, and their implementation brings special challenges and hindrances with it [1]. Using a complex intervention is particularly demanding; the new Medical Research Council guidance specifies how a complex intervention should be developed, established and reproduced [2] and there are also special requirements regarding the quality of the reporting of such studies [3].

Careful and pragmatic planning under everyday conditions in compliance with the relevant international quality standard (ICH-GCP guideline [4]) is crucial for the quality of an RCT. Continuous monitoring in the study centres serves on the one hand to guarantee the rights of the study participants, for example checking that ethically sound informed consent is carried out and written informed consent is obtained. On the other hand, the quality of the data must be guaranteed through randomization in line with the study protocol, careful and valid data collection, also recording adverse events [5], and a follow-up that is as complete as possible. Unforeseen challenges must be anticipated when implementing RCTs [6], meaning that problems in the course of the study must be recognized in good time and that appropriate solutions must be continuously developed, applied and re-evaluated. Furthermore, when applying a complex intervention, it is important to evaluate the process to identify hindrances and challenges which might exist regarding the implementation of the study under everyday conditions, the practicability of the intervention and its acceptance by staff and patients [2].

Well known problems in the implementation of RCTs

When planning RCTs, also multicentre RCTs, it is frequently underestimated that the actual number of recruited study participants can often be distinctly lower than the number calculated as the monthly recruiting rate [7, 8]; this can lead, in the worst case, to failing to achieve the recruitment target resulting from the power calculation. Specific challenges exist for RCTs conducted in delivery rooms: large teams of midwives and obstetricians work together, which means that there is not just one "principal investigator" conducting the study intervention but that the whole team in the obstetric unit is involved in implementing the study. Moreover, women arrive in the delivery room 24 hours a day, seven days a week and this can result regularly in "peak hours" with bed shortage and a high work burden for the whole team.

Due to heterogeneous healthcare systems, different conditions exist internationally regarding the spectrum of tasks, the cooperation between midwives and obstetricians, and the procedures within the actual birthing room. Furthermore, the views and preferences of pregnant women can also differ, i. e. their decision-making awareness, their knowledge about the point and purpose of the research and their motivation to take part in a study.

As pointed out by Vedelø and Lomberg in their review [9], the predominant challenge for researchers conducting RCTs is to ensure that the implementation of the standardized intervention is consistent in all of the study centres, taking the different framework conditions there into account as well as the fact that the involved nursing staff may have no experience of conducting clinical studies. To implement RCTs successfully and in line with the study protocol, the staff has to be convinced of the reason for the study; understandable, practical solutions, which motivate the staff to participate in the study, must be provided so that they can explain the conditions of the study and carry out the randomization and documentation. The authors therefore recommend that research teams carrying out RCTs under challenging conditions should publish their experiences in dealing with challenges and hindrances in order to promote the implementation of future studies [9]. Such publications would inform particularly new researchers and encourage them to reflect both on concrete, quality-relevant challenges and on implementation strategies with an eye to the future. This could also improve their chances when applying for funding for RCTs.

Midwives in German maternity hospitals have frequently little experience as investigative midwives in clinical trials. Even internationally, experience with RCTs on complex interventions in maternity hospitals is not well developed in every country. An orientation search in PubMed revealed the following: In the years 2010 to 2020, findings that of 61 RCTs were published in which a complex intervention was conducted in a maternity ward in a hospital; of these RCTs only 13 were conducted multi-centrically in 2 to 41 hospitals with n=116 to n=12.227 participants [10-22], 2 of which were transnational. For this reason and with regard to supporting junior researchers it is particularly important to share experiences made with RCTs with the professional community, as for example in maternity hospitals in Germany.

Maternity care in German hospitals

Maternity care in Germany is characterized by centralization and insufficient personnel: in the past 20 years the number of maternity hospitals in Germany has been reduced by 36% [23] and at the same time, the number of births increased by 16% [24]. The workload is high for hospital midwives and an average of 1,9 positions per hospital are vacant [25]. Obstetric care is also characterized by high intervention rates [26]: in 2019 the rate for labour induction was 22%, oxytocic drugs were administered in 25% of all the births and 31% of all pregnancies ended with a caesarean section [27]. Based on the country-specific context, this article describes the unexpected challenges that confronted the study team during the course of the clinical trial “BE-UP” despite careful planning, and presents strategies for solving them which have been proven in daily practice.

1. Overview On The Rct “be-up”

The *BE-UP trial* (acronym for *Birth environment – Upright position*) is based on four Cochrane Reviews [28-31] and a pilot study from Canada [32] and is an active controlled superiority trial with a two-arm parallel design [33]. Its aim is to increase vaginal births (VB) and, specifically, to test the effect of a redesigned birthing room (intervention) in hospitals on the probability of VB. By increasing VB, the rate of

caesarean sections will be reduced, which in Germany is higher as would be expected [34], and is associated with increased maternal and infant morbidity. This trial is also in line with the *International Childbirth Initiative's* principles of Mother-Friendly Care [35], the Guideline by the *National Institute of Health and Care Excellence* [36] and the *International Confederation of Midwives* [37] calling for the provision of a birth environment in hospitals that fosters normal births. It is also in accordance with the Royal College of Obstetricians and Gynaecologists' (RCOG) recommendations regarding the equipment of birth rooms [38] and the recently proclaimed 9th German national health goal "Health in Childbirth" [39].

The complex intervention 'redesigned birthing room' contains specially designed features which are absent in the control birthing room. The normal birthing bed, which is otherwise in the centre of the room, is either covered over or removed from the room (figure 1 "BE-UP birthing room at Paracelsus Hospital Henstedt-Ulzburg; permission granted by "Paracelsus Klinik Henstedt-Ulzburg").

Instead, the setup consists of a floor mat, a 40 cm thick mattress and five foam elements (two cubes, one roll, one birthstool-cushion, one back cushion). In addition, there is a beanbag, a monitor showing nature scenes, a dimmable floor lamp, a sitting area with a table and two chairs, and a snack bar with hot and cold drinks and sweet and/or savoury snacks. Each room also has three photo posters showing women in various upright postures. According to experienced midwives and various studies [40, 41], the individual components provide the birthing mother with opportunities for self-determination, relaxation and distraction, so that she feels motivated to move around and stay in an upright position.

The changed setup is intended to improve the physical and emotional client-centred outcomes, a higher self-determination during birth, as well as fewer medical interventions, fewer subsequent CS in future pregnancies and lower healthcare costs for interventions. The statistical calculation included a power of 90% with 5% significance level and a dropout rate below 10%. An increase of VB by 5% from a baseline value of 72% (421,241 VB in hospitals in Germany) to 77% would result in an additional 21,062 women per year, who experience a VB instead of a CS.

Primiparae and multiparae with a singleton foetus in cephalic presentation at term, who are planning a VB, are randomized individually and centrally controlled via online application. Data are collected at admission, during and after birth as well as at three months postpartum; data verification on site (hospitals) is done by external monitors; data management is carried out by an independent coordination centre for clinical trials. To monitor the standard implementation of the study protocol, to identify challenges and problems early on, and to establish a participating relationship for constructive problem solving, visits every 2 months by members of the study team were arranged.

The BE-UP study started in 2017 in 12 maternity hospitals. Based on the total sample size calculation and the number of possible participants who might be recruited per month and participating hospital, it was decided to contact only those maternity hospitals dealing with at least 800 births per year. Recruitment started in April 2018. During the study, 6 hospitals dropped out for various reasons (change of leadership, poor recruitment of study participants, unfilled posts for midwives and physicians, building

reconstruction); therefore, and with the aim of boosting the lagging recruitment rate, the number of participating hospitals was increased to 17. Also, the recruitment period was extended by 15 months until 31 May 2021.

2. Project-related And Process-orientated Challenges For Hospital Staff

During the course of the study, challenges emerged in five sectors that are reflected as follows: 1) Selection of and support for cooperating hospitals; 2) Establishing a process of requesting informed consent; 3) Individual, digital real time randomization; 4) The standardized birthing room; 5) GCP-compliant documentation. In each following section, the relevant initial conditions in the participating hospitals will be outlined before the challenges are named and solution strategies are presented.

2.1 Selection of and support for cooperating hospitals

In Germany, midwives are authorized to conduct physiological births. They support and care for the birthing mothers independently in hospitals and cooperate with an obstetrician in pathological incidences. Midwives working in maternity hospitals generally have a high workload; nearly two-thirds of all midwives regularly look after three birthing mothers at the same time during one shift; in about a third of their shift they deal with unrelated additional work such as cleaning and are only seldom able to take a break; due to the poor working conditions, staff shortages prevail in many places since no applications for the vacant posts are made [25].

Challenges:

The challenge in the BE-UP study was to find hospitals where the rate of vaginal births was relatively low and thus potentially capable of improvement. Moreover, the staff there had to be sufficiently motivated to want to achieve this improvement. Since at least the BE-UP birthing room plus one other normal birthing room are required in order to carry out individual randomization, the hospitals must at the same time have an adequate number of birthing rooms available in comparison to the number of births. Furthermore, the layout of the normal birthing rooms (as the control group), in which many hospitals in Germany provide such things as pezziballs, ceiling ropes and birthing stools, should be clearly distinguishable from the BE-UP birthing room in order for the effect of the complex intervention to be examined properly.

Considering that the study can only be successfully implemented if the whole team has developed sufficient motivation to want changes in obstetrics to take place, it was important to find out whether an effective cooperation existed between midwives and physicians and whether they were interested in the study. This was difficult for the study team to recognize, especially if the head physician was very impressed by the study. In such cases, the midwives might feel patronized. In addition, thought had to be

given to how personnel with little experience of clinical trials should be supported in conducting the study and their motivation strengthened during the study's 36 months duration.

Solutions:

In many cases, the first contact was made via the head midwife. Apart from the number and size of the birthing rooms and the staff situation, we requested obstetrical data from the hospital's perinatal report.

To inform the personnel about participating in the study, staff meetings were held during which the study team presented the study and responded to questions. After the cooperation contract had been signed, several introductory events were held in each hospital in order to save their time resources, despite considerable expenditure of time and money for the study itself. During the course of the study, staff meetings and further training sessions were also used to instruct new staff members. Since financial resources are limited in a publicly funded study, an expense allowance of 20 Euros per study participant was planned as an incentive for the hospital, which was intended to compensate for the expenditure of one additional hour required for informing the study participants and the documentation of the additional study data; however, this compensation had little effect because only seldom was the obstetric unit's staff allowed to have it at their own disposal. We informed the staff about new announcements concerning the study, gave them helpful tips and tricks via email and the password protected study website. We also coordinated press announcements for the hospitals when the 100^{th} or 250^{th} baby was born within the BE-UP trial, all with the intention of providing continuous support and motivation to recruit women for the study.

During the course of the study, the study team organized several one-day study meetings for representatives of the staff in all of the BE-UP hospitals to facilitate interaction between them and to promote a sense of community and identification with the study. To raise the participation preparedness, travel and meal expenses for two people of each hospital were reimbursed from the study's budget. The study team also presented interesting reports in regular newsletters for the hospitals' obstetrical teams (e. g. managing a shoulder dystocia in upright maternal posture). Moreover, the participating hospitals were informed every month via email about the current recruitment situation.

2.2 Establishing a process of requesting informed consent

In Germany, pregnant women are free to choose whichever hospital they prefer for birth, but in most gynaecological practices the women are advised to sign up in a hospital in the close vicinity. Information about the hospitals and the care they provide can be obtained from the respective website or at information events. Expectant parents often visit antenatal classes held by freelance midwives or attend parenting classes in a hospital. Since most of the pregnant women are registered for giving birth in a hospital where a patient's record is also set up, fundamental data about the women are already available when they arrive for the actual birth. Then they can be informed about the BE-UP study and taken to the

birthing room in good time. In contrast, there is not always sufficient time to refer to the BE-UP study during the medical-diagnostic activities in special obstetrical risk consultations.

Challenges:

In the busy everyday hospital routine, the challenge for the BE-UP study centres is to draw the attention of all potential study participants – i. e. all pregnant women with a singleton pregnancy - at an early stage to the possibility of participating in the BE-UP study. Only then would the women have enough time to give their informed consent in writing. The Corona pandemic has complicated matters because the normal information meetings and antenatal classes were cancelled for weeks and pregnant women could register for birth only over the phone.

Solutions:

Comprehensive information for potential study participants was prepared and presented on the study website. There, the study centres were listed and explanatory materials approved by the ethics committee, i. e. information about study participation and informed consent for pregnant women, were made available for download (www.be-up-studie.de). All the text and image material was compiled with help and participation of user representatives. With the aim of relieving the hospital staff and supporting recruitment a multiple strategy was realized, consisting of printed materials (QR code, information card, flyers, website), each with increasingly more detail. When it was seen that recruitment was rather slow, the study team sent out QR code information cards and flyers to the gynaecological practices and midwives in the vicinity of the hospital, asking them to pass the information on to their pregnant patients.

In order to help pregnant women understand the information about the BE-UP study more easily, the study team commissioned two short films, one explaining the scientific target of the BE-UP study and one showing the process of participating in the study from the perspective of the women. The films were presented on the hospitals' websites, on the study website, and in some cases also in the obstetric units' waiting-rooms. To help the maternity staff to respond to occurring difficulties, some practical assistance was developed: a laminated page with the inclusion and exclusion criteria, a short text for focused consultations with the pregnant women who had not heard about the study when they arrived for the actual birth, and BE-UP stickers with the study website's URL, which could be stuck in the pregnancy record book (Mutterpass) to remind an interested woman of the study, or else in their hospital record to indicate that she intends to participate in the BE-UP trial.

From the start of the study, the team was in close contact with the hospital IT departments until their websites had been set up satisfactorily with information about the BE-UP trial. During the course of the study, the IT departments added links on the hospital website to reach the study website, particularly the short films and special information about the situation in the Corona pandemic. The study team's advice that being a BE-UP hospital would have a positive impact on its public relations image was warmly received not only at the beginning of the study. When certain milestones were achieved, for instance the

hundredth birth within the BE-UP study, the press announcements for the hospitals were adjusted appropriately, uploaded to the hospital s websites and also sent to the editors of local newspapers.

2.3 Individual, digital real time randomization

When a pregnant woman arrives in the hospital to give birth, the first examination usually takes place in the admission room. Normally, she is then taken to a birthing room which she cannot select herself.

In the case of study participation, the inclusion and exclusion criteria are additionally checked, any remaining queries from the potential study participant are clarified, the completeness of the written informed consent is checked, and the midwife or physician confirms with his/her signature that the woman has been adequately informed. Then a digital real-time randomization is conducted – a proven procedure provided by the University's Coordination Centre for Clinical Trials that also handles the data management of the BE-UP study. When the allocation to either the intervention group or the control group has taken place, the woman is taken to the corresponding birthing room.

Challenges:

The individual randomization in the BE-UP study does not refer to a single intervention but to an entire space, i.e. birthing environment (complex intervention), and is subject to special requirements: first, both the BE-UP birthing room and another normal birthing room must be vacant so that the random allocation to the intervention or control group can take place. Second, when taking part in the study, the women cannot choose a room, even if two rooms are vacant at the same time. For ethical reasons this might be perceived as being problematic because in recent years the self-determination of a birthing woman during the actual birth has been increasingly recognized and furthered.

Since there is a limit to the number of available birthing rooms (frequently all the rooms are occupied in the everyday life in a clinic), the staff has to undertake an effective room management. This means that the BE-UP birthing room has to be cleaned as quickly as possible so that it is available for randomization. Moreover, for a participant to be included in the study, as many of the midwives as possible should be instructed about the study so that the study implementation can take place with the specified accuracy and fidelity, and the data collection requirements are also fully met in cases where a colleague has to take over when shifts change. Lastly, during the recruitment period, randomization problems due to the absence of an online connection or to operational deficiencies of the randomization software needed a precautionary solution.

Solutions:

We recommended the midwives to arrange for the BE-UP birthing room to be the last one occupied and to use it primarily only for the study so that as many randomizations as possible can be made. In order to ensure this despite a large number of part-time employees, designated contact persons for BE-UP took on the task of specifically checking at shift begin whether a woman could be included at that particular time.

To increase the willingness of pregnant women to take part in the study, the study team asked the staff to emphasize that nobody knew which room was better for the woman and that she had a 50% chance of giving birth in the BE-UP room. It is, however, essential that the women are informed that they can assert their wishes regarding upright body posture and mobility in each birthing room and that the predefined quality standards for care in the hospital will be adhered to, signifying that disadvantages are not to be expected due to randomization.

At the beginning of the study, each of the hospitals were given an iPad for carrying out the randomization. In the course of the study, it was found that there were often less inhibitions and difficulties if their own online devices, such as smartphones or one of the obstetric unit's computers, were used. Six sealed opaque emergency randomization envelopes were additionally provided so that the staff had an alternative, should problems occur during online-randomization; in this way, no potential study participants would be lost.

2.4 The standardized birthing room

Generally, birthing rooms in German maternity hospitals have a "technological" setup [42]. In the centre of the room is an electrically adjustable birth bed, there is a surgical lamp, an emergency anaesthetic unit, a paediatric care unit with a heat lamp as well as a sink and cupboards for storing material. Quite often there is a pezziball, a rope hanging from the ceiling and/or a birthing stool. The lights can be centrally dimmed and, if requested, the staff can provide drinks or snacks.

Challenges:

While the study was being conducted one of the birthing rooms in each hospital was set up as a BE-UP birthing room. An integral part of the BE-UP-concept is that the birth bed is concealed by a paravent, or is absent, thus creating a large contrast to the normal birthing rooms. The elements in the BE-UP birthing room (complex intervention) were designed in cooperation with midwives and patient representatives to conform optimally to the needs of a birthing mother requiring upright posture and mobility, distraction, relaxation and self-determination. In doing so, it must be ensured that the new setup fulfils the hygiene standards and that the staff can work in the BE-UP birthing room according to the hospital□s own standards. The hospitals had to cover only a small share of the costs for equipping the BE-UP birthing room; the larger share was financed by the research's sponsor. Particularly challenging aspects of equipping the rooms as BE-UP birthing rooms in the hospitals were: the limited size of the rooms (very little space for a mattress, floor mat, table and chairs), the built-in power and functional cables for the birth bed, frequently insufficient room for the birth bed outside the birthing room, the restricted manageability of the heavy floor mattress, the possibility of the foam elements slipping on the floor mat, the cool surface of the mattress and midwives' complaints about backache.

Solutions:

To encourage the acceptance of the changes being made when setting up the BE-UP birthing rooms in the cooperating hospitals, we adopted a strong collaborative approach: the hospital staff were able to select the colours for the floor mat, mattress, foam elements, beanbag and chairs in order to achieve a good match with the existing colour concept in the birthing room. To accommodate the cramped space, we also offered a smaller table.

From the start of the study, the study team endeavoured to effectively support the hospital staff: for the new work with upright birthing postures, the hospital was given excerpts from the e-book “The physiological birth” on the iPad as well as the new edition as a printed copy. To stop the foam elements from slipping, the team provided anti-slip material for once-only use and to make the mattress surface more pleasant special terry-cloth sheets were provided. When the midwives in the BE-UP room complained about backache, during one of the study meetings special training in back-saving midwifery work was offered. And to offer teams greater confidence in handling a shoulder dystocia with the birthing woman in an upright position, we had a recognized expert develop a handout, a laminated copy of which is available in the BE-UP room.

2.5. GCP-compliant documentation

Many hospital midwives are very discontented with their jobs; the reasons are manifold – no breaks, habitual overtime and standing in for others as well as unrelated additional work [25, 43]. Above all, the high amount of documentation, which accounts for about 10 percent of the daily workload, is a particular strain on day-to-day working life; the midwives are frequently only able to do the necessary documentation when their shift is over [25] and this has increased in recent years [43].

Challenges:
In a clinical trial the documentation of data should correspond to the guidelines of “good clinical practice” (GCP) and the respective demands are high; in obstetrical hospitals in Germany, documentation is normally digital but various types of documentation and administration software are in use. This means it was impossible to get a homogeneous digital documentation of routine data for use in the trial; at the same time, responsibility for documentation software rests with software providers based on legal contracts, and access to documentation software is linked to hospital-specific routines.

Solutions:

Since the study team did not want to burden the hospital staff with additional unfamiliar documentation software, the case report forms (CRF) comprising routine obstetrical data as well as additional trial-related items were prepared in printed form.

Simultaneously, the study team explored the possibility and willingness of the software providers to supplement the existing hospital software with a “module” for the BE-UP study in order to avoid double documentation and to keep the time required for the trial’s documentation as low as possible.

Upon request and within the frame of their service contract, the developers of the software systems GeDoWin®, Viewpoint® and Nexus® prepared a solution for the automatic transfer of routine data into a digital BE-UP case report form. Thus, about 50% of the approximately 100 items could be incorporated in the CRFs at the push of a button. In eight of the 17 participating hospitals there were either system-specific IT hurdles or work organizational, hospital-specific hurdles, or else the team opted for handwritten documentation.

Multi-stage monitoring was implemented to check on the data quality: monitoring visits every four weeks served to check the ongoing recruitment process and to inspect and validify the data in the CRFs before sending them to the Coordination Centre for Clinical Trials. The Lead Monitoring Officers, who are always easily reached by telephone, visit the hospitals every two months to check whether the complex intervention is being implemented according to the study protocol, whether recruitment is running as planned, and to deal with any special cases or challenges. Finally, they handled any enquires resulting from the plausibility checks of the Coordination Centre for Clinical Trials that it undertook in the course of its query management.

3. Discussion

In this article, the key challenges facing the implementation of a multi-centre RCT's complex intervention in maternity hospitals were presented and pragmatic solution strategies were outlined. The study team applied them a priori and during the course of the study, thus ensuring a GCP-compliant implementation as well as achieving the calculated sample size - even though only when the recruitment phase had been extended.

The application of effective project management strategies is essential for an RCT to be conducted successfully [44]; this article expands and specifies this knowledge in relation to an RCT in maternity hospitals staffed by midwives and obstetricians, most of whom have little or no research experience. Future groups of researchers are thus supported when planning RCTs in maternity hospitals with similar settings. A thorough reflection on the components and their design is important in the **conception of complex interventions** [45] in order to achieve sufficient contrast to the control intervention, taking interactions during obstetrical care and contextual conditions into consideration [41, 46-48]. In addition, the opportunity for the hospital staff to assert their personal preferences, such as the desired colour of various intervention components, strengthens both motivation and commitment.

The careful **selection of the study centres** is of fundamentally high importance when planning an RCT [49]. Besides objective care data such as number of obstetric cases, heterogeneity of clients and regional location, in the field of obstetrics the available facilities and hospital-specific care processes are highly relevant for assessing the feasibility of implementing a trial. In hospitals where no appointments are given for consultation and birth enrollmentit is difficult to impart trial information to the pregnant women early enough. A high proportion of part-time staff can be an impediment to establishing implementation routines within the team, such as the continuous appraisal of everyday situations regarding available

rooms and personnel, which is a prerequisite for the continuing enrolment of study participants. Moreover, the lack of research experience and a high workload within the obstetrical team can result in not all the potential study participants receiving the required explanations about the study and therefore are not included in the trial. Staff with little research practice can profit from practical exercises and concrete phrasing suggestions, for instance when the woman is already in labor.

The BE-UP's multimodal information concept with increasingly detailed information for potential study participants that was developed participatively has fulfilled its purpose. User representatives were involved in the entire planning and implementing process so that the content is presented in a relevant, appealing and easy-to-understand way that is focused on women [50]. The production of low-budget, 5-minutes long video films were worth the extra expenditure: both of the short films were accessed around 300 – 400 times each month, confirming that even in obstetrical settings videos are yet another way of presenting information about clinical studies [51]. This was confirmed all the more when the normal face-to-face information meetings, antenatal classes and birthing enrolments were suspended due to the COVID-19 pandemic; the numbers of users accessing the videos and the additional short audio files then increased by around a third.

With regard to **the randomization of study participants**, the most important reason for difficulties in this direction so far was the overestimation of the potential number of includable pregnant women in the planning stage of an RCT, resulting in a required extension of the recruitment period [7, 52]. The planned monthly recruitment figures per hospital in the BE-U study were based on the assumption that every two days a woman could be enrolled for the BE-UP study, a cautious estimation made by international colleagues. However, despite careful overall planning, unforeseen events occurred which impeded recruitment, in particular the closing down of other hospitals in the vicinity and the resulting unexpected increase of births in the BE-UP hospitals with the consequent persistent lack of space. All in all, the recruitment curve in the first few months of the study grew very slowly, demonstrating that a lot of time is needed on the part of the obstetrical teams to deal with the processes of change and adaptation. In addition, it took a longer time to motivate many of the midwives and physicians for the study. Other reasons for the slow recruitment were staff shortages and pregnant women who did not have adequate knowledge of the German language. Later on, the lock-down measures of the COVID-19 pandemic impeded the early access to potential study participants. During the recruitment phase it was foreseeable that six hospitals could not increase their very low recruitment numbers, so that they had to be withdrawn and a large number of new hospitals had to be found in order to increase the recruitment rate. Finally, the recruitment period had to be extended by 15 months to attain the targeted number of study participants.

As was determined in a qualitative evidence synthesis, the recruiting of study participants is also influenced by the personalities of the recruiters themselves: through their own beliefs and power, they act as gatekeepers [53]. In the BE-UP study, higher recruitment numbers were not achieved in hospitals where some of the midwives were unable to accept the new conditions, such as midwifery care without a birth bed. The recruiters themselves can experience intellectual and emotional conflict if they are confronted with a contradictory situation resulting from their hospital work and their simultaneous role as recruiters

[54]. For instance, in BE-UP the midwives might find themselves in a conflict of roles if they have to conduct an explanatory interview about the study when the mother is already in labour. Even denying a mother her wish to use the BE-UP room without participating in the study or having to hand over the woman's care to a colleague can also be experienced as conflictual. The experiences gained by the midwives during the study as well as their courses of action are currently the subject of qualitative studies.

The practical implementation of the real-time block **randomization of study participants** was technically very well planned and implemented. However, the use of an on-line randomization service was hampered if the hospital staff had little or no experience of using digital ways of communication. The additionally offered emergency randomization envelopes with concealed group allocation therefore allowed a low-threshold solution for situations in which the on-line connection could not be established or digital randomization did not work for other reasons.

At the beginning of the study and in the interest of cooperative partnership, the study team was eager to enable hospitalstaff to have a say in the decision-making, for instance when selecting the colours for the mattresses, foam cubes and towels. During the 2-monthly visits to the hospitals, the study team developed strategies for an effective cooperation between themselves as researchers and the hospital staff [9] in order to support the obstetrical team constructively in coping with everyday hurdles and to strengthen their motivation to recruit study participants. In the process, it was possible to develop and maintain a supportive and positive relationship with the contact persons in the hospitals, which was characterized by empathy, appreciation and commitment. For this to be convincing, the study team must have a high level of social competence and expertise. In BE-UP, weekly meetings in the study centres were not possible for a total of 17 hospitals – contrary to the recommendations of other studies [55]. Instead, we held alternating regional and central study meetings with representatives from the hospitals, which took either half a day or a whole day, and which were well attended. The participants greatly appreciated the opportunity to exchange experiences among themselves.

To ensure a **GCP-conform documentation**, the principles "collect only as much data as necessary", "simplicity in implementation" and "best possible adaptation to existing documentation routines" were applied. The study team was advised and supported here by the independent Coordination Centre for Clinical Trials, which was responsible for data and query management. During the intensive on-site monitoring, the data could be checked for completeness, correctness and readability in cooperation with the staff, and query forms from the Coordination Centre for Clinical Trials filled in. The cooperation with three providers of software used in a total of 8 hospitals was helpful to the respective staff.

The monetary allowance to compensate staff for the extra work in informing study participants and for the additional documentation was too low in the BE-UP study to be an effective incentive for recruitment, especially since these amounts were not available to maternity staff in all of the hospitals.

4. Conclusions

Research groups who are planning RCTs in maternity hospitals in settings with only a few midwives and physicians with research experience should carefully check the factors relating to work organization and personnel that might influence the local recruitment of study participants. In future studies, especially in such a setting, recruitment should be estimated more conservatively. When applying for an RCT and in view of the setting of the study, the principal investigator and the study team should conduct a careful and forward-looking analysis and reflection of the framework conditions of everyday maternity care in order to anticipate possible challenges in the practical implementation of an RCT. Yet not all challenges can be anticipated in the planning of a study, therefore the study team needs to be flexible and must react promptly to any problems that threaten recruitment or the required implementation of the complex intervention.

Together with the staff from the participating hospitals, thought should be given to how clinic-intern processes that are relevant for conducting the study could be adapted to correspond with the study's requirements. This would provide the opportunity to plan for adequate resources in the application for funding right from the start. Future research projects could examine in more detail the perspectives of midwives as recruiters and determine the concerns which inexperienced midwives and physicians might have regarding carrying out informed consent as well as how role conflicts might be eased that hamper the recruitment of study participants [56].

Declarations

Ethics approval: The ethics committee of the Medical Faculty of Martin Luther University of Halle-Wittenberg in Halle (Saale), Germany, approved the study protocol and the information material for informed consent (committee`s reference number 2017-140). Also, the federal states' ethical committees responsible for the medical doctors employed at the participating hospitals approved the conduct of the study. All participants provided informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Funding: The BE-UP study is financed by the Federal Ministry of Education and Research The clinical trial is sponsored by the Federal Ministry of Education and Research (funding code (FKZ) 01KG1715).

Trial registration: The BE-UP study was registered 7 March 2018 in the German Register for Clinical Trials under the Reference No. DRKS00012854 and can also be found on the International Clinical Trials Registry Platform (ICTRP) (see https://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS0001285).

Availability of data and materials: not applicable

Authors contribution: SS conceptualized the manuscript and coordinated the finalisation, EM contributed to the challenges regarding the selection of study centres and GCP-compliant documentation, TO contributed to the challenges regarding informed consent and randomization, and RS and GA contributed to the description of the BE-UP study and the challenges pertaining to the BE-UP birthing room. All

authors together improved the description of the entire content and read and approved the final manuscript.

Consent for publication: Maren Maak of Paracelsus Hospital Henstedt-Ulzburg gave the consent for publication the figure 1.

Competing interests: The authors have no competing interests.

Acknowledgements: The study team wants to thank all midwives and obstetricians in the participating hospitals for recruiting study participants. We thank Mrs. Vivienne Krause for translating the manuscript into English language.

Author's information: All authors are midwives and members of the study team. GA is the prinicpal investigator of the study at Martin Luther University Halle-Wittenberg, RS is the coordinating investigator at the University of Applied Science, Bochum. ST, EM and TO are regional trial managers and lead monitors.

References

1. Duley L, Antman K, Arena J, Avezum A, Blumenthal M, Bosch J et al. *Specific barriers to the conduct of randomized trials*. Clinical Trials. 2008; 5: 40–48. DOI: 10.1177/1740774507087704
2. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth S, Petticrew P. *Developing and evaluating complex interventions: the new Medical Research Council guidance*. BMJ. 2008. **337**: p. a1655. Doi: 10.1136/bmj.a1655
3. Möhler R, Köpke S, Meyer G. *Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2)*. Trials, 2015. **16**, 204. DOI: 10.1186/s13063-015-0709-y.
4. European Medicines Agency. *Guideline for good clinical practice E6(R2)*. 2016.
5. UK Trial Managers Network (UKTNM). *The Guide to Efficient Trial Management - Effectively managing clinical trials*. 2016.
6. Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt S, et al. *Barriers to the conduct of randomised clinical trials within all disease areas*. Trials, 2017. **18**, 360 DOI: 10.1186/s13063-017-2099-9.
7. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies.* Trials, 2006. **7**: p. 9. *DOI:10.1186/1745-6215-7-9*
8. Sully BGO, Julious SA, Nicholl J. *A reinvestigation of recruitment to randomised, controlled, multicentre trials: a review of trials funded by two UK funding agencies*. Trials, 2013. **14**.
9. Vedelo TW, Lomborg K. *Reported challenges in nurse-led randomised controlled trials: an integrative review of the literature*. Scand J Caring Sci, 2011. **25**, 194–200 DOI: 10.1111/j.1471-

6712.2010.00816.x.

10. Levett KM, Smith CA, Bensoussan A, Dahlen HG, et al.,*Complementary therapies for labour and birth study: a randomised controlled trial of antenatal integrative medicine for pain management in labour*. BMJ Open, 2016. **6**(7): p. e010691. DOI: 10.1136/bmjopen-2015-010691
11. Grooten IJ, Koot MH, van der Post JA, Bais JM, Ris-Stalpers C, Naaktgeboren C et al. *Early enteral tube feeding in optimizing treatment of hyperemesis gravidarum: the Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding (MOTHER) randomized controlled trial*. Am J Clin Nutr, 2017. **106**(3): p. 812–820. DOI: 10.3945/ajcn.117.158931
12. Larsson B, Karlström A, Rubertsson C, Ternström E, Ekdahl J, Segebladh B. et al. *Birth preference in women undergoing treatment for childbirth fear: A randomised controlled trial*. Women Birth, 2017. **30**(6): p. 460–467. DOI: 10.1016/j.wombi.2017.04.004
13. Perales M, Calabria I, Lopez C, Franco E, Coteron J, Barakat R. *Regular Exercise Throughout Pregnancy Is Associated With a Shorter First Stage of Labor*. Am J Health Promot, 2016. **30**(3): p. 149–54. DOI: 10.4278/ajhp.140221-QUAN-79
14. Clements V, Leung K, Khanal S, Raymond J, Maxwell M, Rissel C. *Pragmatic cluster randomised trial of a free telephone-based health coaching program to support women in managing weight gain during pregnancy: the Get Healthy in Pregnancy Trial*. BMC Health Serv Res, 2016. **16**(1): p. 454. DOI: 10.1186/s12913-016-1704-z
15. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN et al. *Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial*. Bmj, 2014. **348**: p. g1285. DOI: 10.1136/bmj.g1285
16. Tohotoa J, Maycock B, Hauck YL, Dhaliwal S, Howat P, Burns S et al. *Can father inclusive practice reduce paternal postnatal anxiety? A repeated measures cohort study using the Hospital Anxiety and Depression Scale*. BMC Pregnancy Childbirth, 2012. **12**: p. 75. DOI: 10.1186/1471-2393-12-75
17. Gau ML, Chang CY, Tian SH, Lin KC. *Effects of birth ball exercise on pain and self-efficacy during childbirth: a randomised controlled trial in Taiwan*. Midwifery, 2011. **27**(6): p. e293-300. DOI: 10.1016/j.midw.2011.02.004
18. Deneux-Tharaux C, Sentilhes L, Maillard F, Closset E, Vardon D, Lepercq J, Goffinet F. *Effect of routine controlled cord traction as part of the active management of the third stage of labour on postpartum haemorrhage: multicentre randomised controlled trial (TRACOR)*. Bmj, 2013. **346**: p. f1541. DOI: 10.1136/bmj.f1541
19. Poston L, Briley AL, Barr S, Bell R, Croker H, Coxon K, et al. *Developing a complex intervention for diet and activity behaviour change in obese pregnant women (the UPBEAT trial); assessment of behavioural change and process evaluation in a pilot randomised controlled trial*. BMC Pregnancy Childbirth, 2013. **13**: p. 148. DOI: 10.1186/1471-2393-13-148
20. The Epidural and Position Trial Collaborative Group, *Upright versus lying down position in second stage of labour in nulliparous women with low dose epidural: BUMPES randomised controlled trial*. BMJ, 2017. **359**: p. j4471. DOI: 10.1136/bmj.j4471

21. Gülmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M et al. *Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial*. Lancet, 2012. **379**(9827): p. 1721–7. DOI: 10.1016/s0140-6736(12)60206-2
22. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S.et al. *The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): Is Severe Hypertension Just an Elevated Blood Pressure?* Hypertension, 2016. **68**(5): p. 1153–1159. DOI: 10.1161/hypertensionaha.116.07862
23. [German Bundestag, Working situation of midwives in maternity hospitals. The German situation in comparison to other European countries. 2019] Deutscher Bundestag, *Zur Arbeitssituation von Hebammen in der stationären Geburtshilfe Vergleich der Situation in Deutschland mit der in ausgewählten europäischen Ländern*. 2019.
24. [German Federal statistical Office – Live births – Variations of number of live births to the respective previous year] Statistisches Bundesamt. *Lebendgeburten - Veränderung der Zahl der Lebendgeborenen zum jeweiligen Vorjahr*. 2020; https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Geburten/Tabellen/lebendgeborene-differenz.html. Accessed 06/06/2020
25. [IGES Institute. Maternity Care in hospitals] IGES Institut, *Stationäre Hebammenversorgung*. 2019.
26. Miller S, Abalos E, Chamillard M, Ciapponi A, Colaci D, Comandé D et al., *Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide*. The Lancet, 2016. **388**(10056): p. 2176–2192. DOI: 10.1016/S0140-6736(16)31472-6
27. [Institute for Transparency and Quality in Healthcare. National evaluation report 2019 Maternity Care.] IQTIG, *Bundesauswertung zum Erfassungsjahr 2019. Geburtshilfe*. 2020.
28. Hodnett ED, Gates S, Hofmeyr GJ, Sakala C. *Continuous support for women during childbirth*. Cochrane Database Syst Rev, 2012. **10**: p. CD003766. Doi:10.1002/14651858.CD003766.pub4
29. Lawrence A, Lewis L, Hofmeyr GJ, Styles C. *Maternal positions and mobility during first stage labour*. Cochrane Database of Systematic Reviews, 2013(10). DOI: 10.1002/14651858.CD003934.pub4
30. Gupta JK, Hofmeyr GJ, Shehmar M. *Position in the second stage of labour for women without epidural anaesthesia.* Cochrane Database Syst Rev, 2012(5): p. Cd002006. DOI: 10.1002/14651858.CD002006.pub3
31. Kibuka M, Thornton JG, *Position in the second stage of labour for women with epidural anaesthesia*. Cochrane Database Syst Rev, 2017. **2**: p. CD008070. DOI: 10.1002/14651858.CD008070.pub3
32. Hodnett ED, Stremler R, Weston JA, McKeever P. *Re-conceptualizing the hospital labor room: the PLACE (pregnant and laboring in an ambient clinical environment) pilot trial*. Birth, 2009. **36**(2): p. 159–66.
33. Ayerle GM, Schafers R, Mattern E, Striebich S, Haastert B, Vomhof M. et al. *Effects of the birthing room environment on vaginal births and client-centred outcomes for women at term planning a vaginal birth: BE-UP, a multicentre randomised controlled trial*. Trials, 2018. **19**(1). DOI: 10.1186/s13063-018-2979-7

34. Betran AP, Torloni MR, Zhang JJ, Gulmezoglu AM, WHO Working Group on Caesarean Section. *WHO Statement on Caesarean Section Rates*. BJOG, 2016. **123**, 667–70 DOI: 10.1111/1471-0528.13526. DOI: 10.1111/1471-0528.13526
35. Lothian JA. *Introduction: the coalition for improving maternity services.* J Perinat Educ, 2007. **16 Suppl 1**: p. 1S-4S. DOI: 10.1624/105812407X173119
36. National Institute of Clinical Excellence. *Intrapartum care - care of healthy women and their babies during childbirth*. 2014.
37. International Confederation of Midwives. *Position Statement: Keeping Birth Normal*. 2014.
38. RCOG. *Safer Childbirth - Minimum Standards for the Organisation and Delivery of Care in Labour*. 2007.
39. [Federal Gazette. 9th National Health Goal. Health in Childbirth. 2017] Bundesanzeiger, *9. Nationales Gesundheitsziel Gesundheit rund um die Geburt*. 2017.
40. Aburas R, Pati D, Casanova R, Adams NG. *The Influence of Nature Stimulus in Enhancing the Birth Experience*. HERD, 2017. **10**(2): p. 81–100. DOI: 10.1177/1937586716665581
41. Manesh MJ, Kalati M, Hosseini F. *Snoezelen Room and Childbirth Outcome: A Randomized Clinical Trial*. Iranian Red Crescent Medical Journal, 2015. **17**(5). DOI: 10.5812/ircmj.17(5)2015.18373
42. Bowden C, Sheehan A, Foureur M. *Birth room images: what they tell us about childbirth. A discourse analysis of birth rooms in developed countries*. Midwifery, 2016. **35**: p. 71–7. DOI: 10.1016/j.midw.2016.02.003
43. Stahl, K. *Work experience and work environment of midwives in German labour wards and implications for the quality and safety of care*. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen, 2017. DOI: 10.1016/j.zefq.2016.07.005.
44. Arundel C, Gellatly J. *Learning from OCTET - exploring the acceptability of clinical trials management methods*. Trials, 2018. **19**, 378 DOI: 10.1186/s13063-018-2765-6.
45. Thomas J, Petticrew M, Noyes J, Chandler J, Rehfuss E, Tugwell P et al. Chapter 1*7: Intervention complexity.* In *Cochrane Handbook for Systematic Reviews of Interventions version 6.0*, Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. (Editors) 2019, Cochrane.
46. Fahy KM, Parratt JA. *Birth Territory: a theory for midwifery practice*. Women & Birth: Journal of the Australian College of Midwives, 2006. **19**(2): p. 45–50.
47. Igarashi T, Wakika M, Miyazaki K, Nakayama T. *Birth environment facilitation by midwives assisting in non-hospital births: A qualitative interview study*. Midwifery, 2014. **30**(7): p. 877–884. DOI: 10.1016/j.midw.2014.02.004
48. Townsend B, Fenwick J, Thomson V, Foureur M. *The birth bed: A qualitative study on the views of midwives regarding the use of the bed in the birth space*. Women Birth, 2016. **29**(1): p. 80–4. DOI: 10.1016/j.wombi.2015.08.009
49. Williams GW. *The other side of clinical trial monitoring; assuring data quality and procedural adherence*. Clinical Trials, 2006. **3**, 530–7.

50. INVOLVE. *Briefing notes for researchers: public involvement in NHS, public health and social care research*. 2012, Involve/NHS: Eastleigh.
51. Hillyer GC, MacLean SA, Beauchemin M, Basch CH, Schmitt KM, Segall L et al. *YouTube Videos as a Source of Information About Clinical Trials: Observational Study*. JMIR Cancer, 2018. **4**, e10060 DOI: 10.2196/10060.
52. Gemmell, Miller P. *Relative effectiveness and adverse effects of cervical manipulation, mobilisation and the activator instrument in patients with sub-acute non-specific neck pain: results from a stopped randomised trial*. Chiropr Osteopat, 2010. **18**: p. 20. DOI: 10.1186/1746-1340-18-20
53. Hanrahan V, Gillies K, Biesty L. *Recruiters' perspectives of recruiting women during pregnancy and childbirth to clinical trials: A qualitative evidence synthesis*. PLoS One, 2020. **15**(6): p. e0234783. DOI: 10.1371/journal.pone.0234783
54. Elliott D, Husbands S, Hamdy FC, Holmberg L, Donovan JL. *Understanding and Improving Recruitment to Randomised Controlled Trials: Qualitative Research Approaches*. Eur Urol, 2017. **72**(5): p. 789–798. DOI: 10.1016/j.eururo.2017.04.036
55. Strong S, Paramasivan S, Mills N, Wilson C, Donovan JL, Blazeby JM. *'The trial is owned by the team, not by an individual': a qualitative study exploring the role of teamwork in recruitment to randomised controlled trials in surgical oncology*. Trials, 2016. **17**(1): p. 212. DOI: 10.1186/s13063-016-1341-1
56. Donovan JL, Paramasivan S, De Salis I, Toerien M. *Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials*. Trials, 2014. **15**. DOI: 10.1186/1745-6215-15-5

Figures

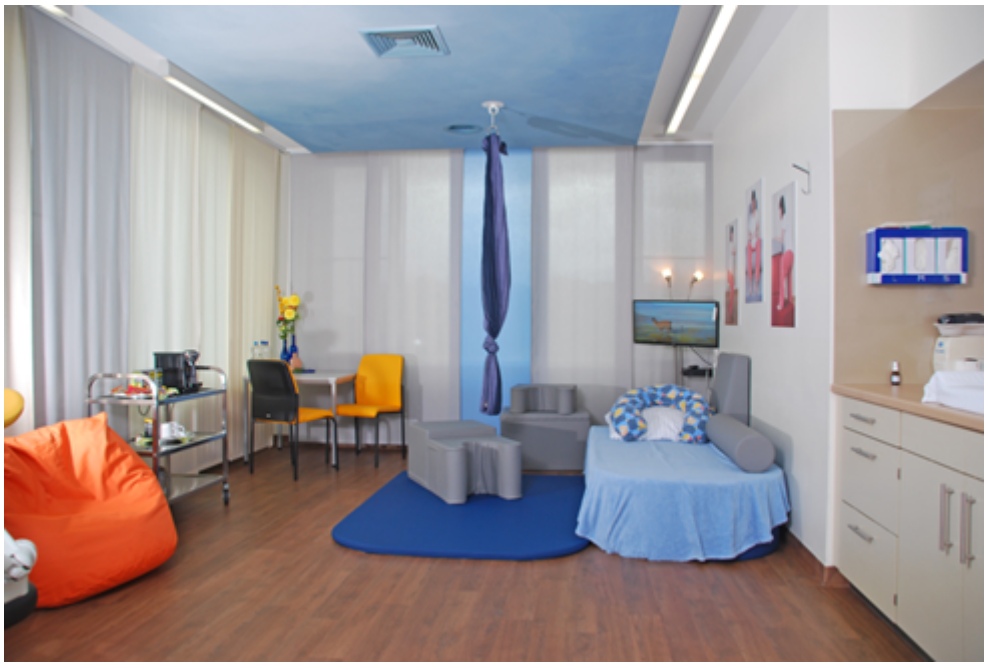

Figure 1

BE-UP birthing room at Paracelsus Hospital Henstedt-Ulzburg; permission granted by “Paracelsus Klinik Henstedt-Ulzburg