Study protocol

Effectiveness of acupuncture for cyclical mastalgia （CM）

CFH2022-3-7132

2022.5.28

Study protocol

Effectiveness of acupuncture for cyclical mastalgia （CM）

1. Participant Flow

Recruitment Details

Patients are planned to be recruited via outpatient clinic, advertisements on websites and posters from hospitals and a chat group using WeChat (WeChat, Version: 8.0.21, Tencent, Shenzhen, China). The recruitment date is from July 1, 2022 to December 31, 2023. The Recruitment location will be performed at three hospitals in Beijing: (1)Beijing Traditional Chinese Medicine Hospital Pinggu Hospital, (2)Pinggu huangsongyu Community hospital, and (3)Pinggu Xiagezhuang Community hospital.
All potentially eligible women with CM will be invited to the trial and be able to contact the researchers with the provided phone number. Eligible participants will be introduced to the research contents in detail and informed about the potential benefits and possible risks of this study, then personal information including age, marriage, menstrual, and medical history are cautiously recorded. After 2 weeks of reflection, patients are invited to meet with the research physician to discuss any remaining questions and sign the informed consent.

Pre-assignment Details

Eligible participants will be introduced to the research contents in detail and informed about the potential benefits and possible risks of this study, then personal information including age, marriage, menstrual, and medical history are cautiously recorded. After 2 weeks of reflection, patients are invited to meet with the research physician to discuss any remaining questions and sign the informed consent.

Arm/Group Information

Arm/Group Title

108 patients will be randomly divided into MA (manual acupuncture)and SA(sham acupuncture) (1:1 allocation ratio)

Arm/Group Description

MA group

Acupuncture rationale was based on the theory of TCM, which is closely related to the liver. When reviewing the literature on breast pain, people believe that "Stagnation of liver qi and stagnation of Qi and blood" is a good explanation for the important mechanism of breast pain attack. We will select Ashi points (the most obvious local pain over the breast), Tanzhong(CV17), bilateral Wuyi (ST15), Rugen (ST18), Tianzong(SI11), Geshu (BL17), Ganshu(BL18), Hegu(LI4), Sanyinjiao (SP6) and Taichong (LR3)in this trial. The location of the above acupoints will be based on the nomenclature and location of acupuncture points drafted by the National Standard of the People’s Republic of China (GB/T 12 346-2006) [1]. Sterile single-use stainless steel needles (size 0.3 mm × 40 mm) (Hwato brand, Suzhou Medical Appliance Factory, China) will be utilized. After local skin disinfection with 75% alcohol wipes while patients are in a sitting position, then fix the adhesive pad (to ensure the implementation of a blind method, the acupuncture group is placed with the same

fixed adhesive pad as the sham acupuncture group). Acupuncturists will insert needles horizontally into the Wuyi(ST15), Rugen (ST18), and Ashi points toward the mammary duct to a depth of 15 – 20 mm; horizontally into tanzhong(CV17) downward to a depth of 5 – 10 mm, perpendicularly into Hegu(LI4), Sanyinjiao (SP6), Tianzong(SI11), and Taichong (LR3) to a depth of approximately 15 – 25 mm. Obliquely into Geshu (BL17) and Ganshu(BL18)to a depth of approximately15-20mm.The depth of needling will vary based on the participant's body size. After insertion, all needles will be manually manipulated (equal manipulations of twirling, lifting, and thrusting)to achieve De qi sensation, which is defined as a composite of unique needling sensations, including soreness, numbness, distention, or heaviness felt by both participants and acupuncturists [2]. All the needles will be retained for 30 min and then gently removed.

SA group

Sham acupuncture rationale was based on taking nonmeridian and nonpoints of ganglion segments different from breast pain area. The SA group will use a special needle in which the tip is blunt and the pedestal is opaque. There is an adhesive pad below the base to ensure that the whole pedestal can adhere to the points. Participants will receive superficial touch at bilateral sham GV8(Jinsuo), sham GV7(Zhongshu), sham GV6(Jizhong), sham GV5(Xuanshu), sham GV4(Mingmen), sham BL37(Yinmen), and sham BL57(Chengshan). ShamGV8, GV7, GV6, GV5,GV4 (≈ 20mm to horizontally outside of GV8, GV7, GV6, GV5,GV4), BL37, and BL57(≈ 10mm to horizontally outside of BL37 and BL57). After local skin disinfection with 75% alcohol wipes while patients are in a prone position, then fix the adhesive pad, and give the patient a verbal prompt to inform the patient of the need for acupuncture manipulation. Sham acupuncture needles of 0.30×40 mm size(Hwato brand, Suzhou Medical Appliance Factory, China) will be inserted the adhesive pad at a depth of 2 – 3 mm until the needles can standstill, the needles will touch the skin and not be inserted into the skin, then lift and twist each point evenly for 3 times, make the subject feel the similar sensation of deqi. All the needles will be retained for 30 min and then gently removed.

All patients will undergo treatment two weeks before menstruation, and treatment will be stopped at the onset of menstruation. Three times a week, six times a menstrual cycle, and 3consecutive menstrual cycles for a total of 18 sessions after baseline. All acupuncturists have a license and at least 5 years of acupuncture practice.Patients will be treated separately with a curtain drawn and their companions waiting outside the clinic. Patients in both groups will receive advice on breast pain education and lifestyle modification. During the process of the trial, patients are not allowed to take other specialized medication or therapies for CM, details should be recorded in the case report form (CRF**).**

1. Standardization Administration of the People's Republic of China. GB/ T12346-2006, Nomenclature and Location of Acupuncture Points [S]. 2006.

2. Zhou K, Fang J, Wang X, et al. Characterization of de qi with electroacupuncture at acupoints with different properties. J Altern Complement Med. 2011;17(11):1007-13.https://doi.org/10.1089/acm.2010.0652

Type of Units Assigned

Period(s)

The duration of the trial is 38weeks for each patient, including a 2-week baseline assessment (week 0-2), 12-week treatment period (week 1-12), and 24-week follow-up (week 13-36).

2. Baseline Characteristics

Personal information including age, marriage, menstrual, and medical history and a series of questionnaire including VAS-BP in the first two weeks of menstruation , the number of nominal days of breast pain (NDBP) two weeks before menstruation, World Health Organization Quality Of Life Scale-Short Form(WHOQOL-BREF) scores, breast glandular section thickness and breast duct width three days before menstruation are cautiously recorded.

3. Outcome Measures

Primary outcome

The primary outcome in this trial is the change in the average of VAS-BP scores in the first 2 weeks of menstruation, recorded in the patient daily diary.

The VAS-BP will be measured using a 10cm linear VAS with 0 representing no pain and 10 the worst imaginable pain from baseline at weeks 4, 8, and12.

Secondary outcomes

1.The changes in the number of nominal days of breast pain (NDBP) during 2 weeks before menstruation from baseline at weeks 4,8,12.

2. The changes of WHOQOL-BREF scores from baseline at weeks 12.The WHOQOL-BREF china version will be used to evaluate the QOL of the participants. The WHOQOL-BREF Questionnaire consists of 26 items, in which the first and second questions of the questionnaire are about the QOL and health status in general. The next 24 questions assess the QOL in four dimensions: physical health (7items); psychological(6 items); environment (8 items); and social relationships (3 items). Each item is answered on a five-point scale. A higher score denotes a better quality of life [3-4].

3. The changes in breast glandular section thickness, and breast duct width three days before menstruation from baseline at weeks 12.

Mammary ultrasonography will be used to observe breast glandular section thickness, and breast duct width. All ultrasound image acquisition work is completed by the same ultrasound physician with at least 5 years of professional practice.

4. Patients' global improvement assessment: It will be assessed by a 7-point self-reporting scale ranging from 1 to 7: significantly reduced, moderately reduced, slightly reduced, no change, slightly aggravated, moderately aggravated, and significantly aggravated. The proportion of patients reporting "significantly reduced" or "moderately reduced" is recorded as the response rate of overall efficacy.

5. Patients' acceptability toward acupuncture at the end of the 1st treatment at week1 and lthe last treatment at week12. The acceptability of acupuncture will be assessed among participants in the MA group using a 3-point index: unacceptable (0 points), acceptable (1 point), and easy to accept (2 points). Those who regard acupuncture as unacceptable will report the reasons. The average score will be calculated after the 2

assessments.

6. Blindness assessment: within 3 min after the last treatment session at week 12, all participants will be asked to answer the question do you think you have received acupuncture treatment and choose the answer between the options of Yes or No.

3. Hao YT, Fang JQ.The introduce and usage of WHOQOL instrument in Chinese.Mod Rehabil.2000;4(8):1127-1129.

4.The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med, 1998;28(3):551-558.https://doi.org/10.1017/s0033291798006667

Statistical analysis

Sample size estimation was based on changes in the breast pain VAS(VAS-BP) score. According to the pre-trial, the VAS-BP score significantly decreased by 2.98 ±0.95 in MA group compared to 2.35 ±0.97 in the SM group after treatment from baseline. In the current trial, we assume a significance level $\alpha = 0.05$ and power $(1-\beta) = 0.90$, and providing for a two-sided outcome, at least 42 participants will be required for each group, as calculated by PASS version 11.0 (NCSS, LLC. Kaysville, UT, USA), assuming a two-tailed test with a 20% drop-out rate, a total of 108 patients (54 in each group) will be recruited.

Data management

The clinical trial management platform ResMan will be used to manage the data. Repeated input methods will be used to ensure that the entered data is correct. The database will be locked with a password, which will only be known by relevant personnel.

Statistical methods

Statistical methods for primary and secondary outcomes

We will use SPSS 22.0 software(IBM SPSS Statistics; IBM Corp, Somers, NY)to perform all statistical analyses following the intention-to-treat principle. The CI will be established at 95%, and the significance level at 0.05. For continuous data, the data will be presented as mean±standard deviation when normally distributed or presented as median (IQR) when not normally distributed. Statistical comparisons will be performed by the independent-sample t tests or Wilcoxon rank-sum test for continuous data and by X2-test or Fisher exact test for categorical data, as appropriate. A p-value <0.05 will be considered statistically significant.

Interim analyses

Not applicable.

Methods for additional analyses (e.g. subgroup analyses)

Not applicable.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

We perform statistical analysis on complete case.The researcher will contact participants as much as possible to supplement missing data. The missing data will be assessed using an intention-to-treat analysis.

Plans to give access to the full protocol, participant level-data and statistical code

The data sharing will be available upon request and with permission and

approval from the Pinggu Hospital of Beijing Traditional Chinese medicine hospital.

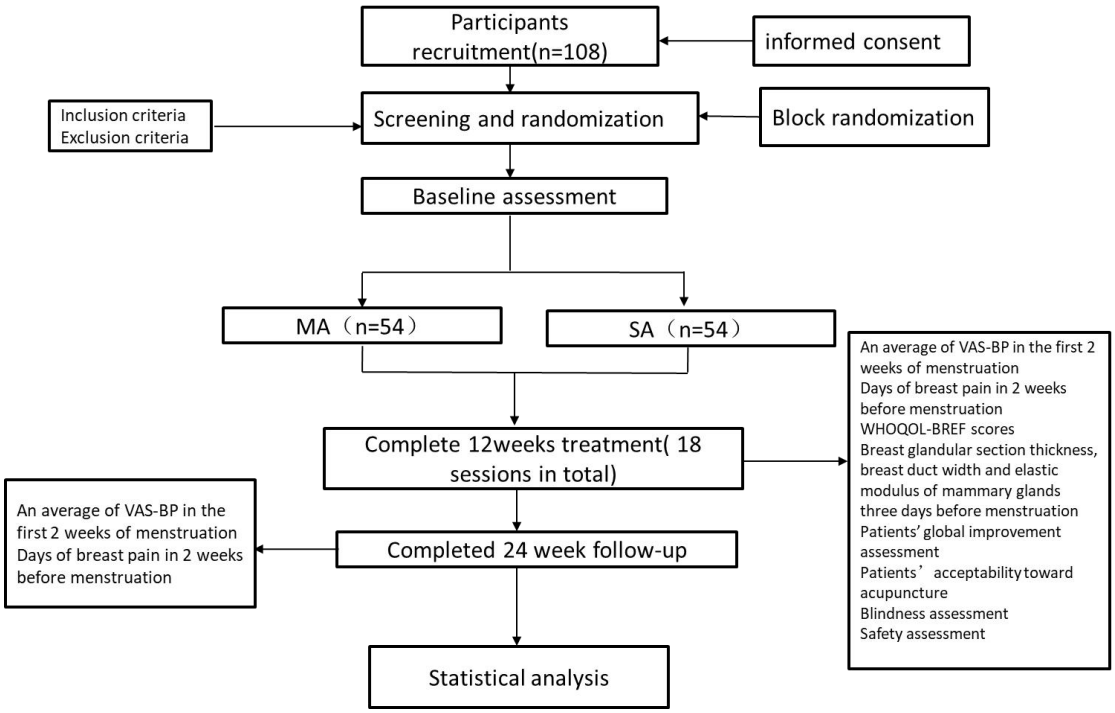
4. Adverse event reporting and harms

All adverse events will be documented in the CRF throughout the trial. Adverse events related to acupuncture (such as severe pain, local hematoma, infection and abscess, and broken needles), including discomfort after treatment, will be recorded in time and detail. A detailed description of the categories, severity and correlation with the treatment of the adverse events will be collected by patients themselves and evaluators. If the adverse event is severe and associated with the trial, the patient will be withdrawn from the study and given appropriate medical care.

5. Results Point of Contact

Yuchuan, Chief physician, Department of Acupuncture and Moxibustion, Beijing Pinggu District Hospital of Traditional Chinese Medicine, 101200, Beijing, China.010-69970907, yuchuan106@126.com

Figure 1. Flow chart of participants through the proposed trial.



The schedule of the whole procedure is shown in Table1

Table1Study period.

	STUDY PERIOD						
	Enrolment	Allocation	Treatment			Follow up	
Timepoint(W,week)	-2	0	4	8	12	24	36
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
Interventions							
Manual acupunture			◆—	—	—◆		
Sham acupunture			◆—	—	—◆		
Assessment							
VAS-BP	X	X	X	X	X	X	X
NDBP	X	X	X	X	X	X	X
WHOQOL-BREF		X			X		
Breast glandular thickness		X			X		
Breast duct width		X			X		
Patients' global improvement assessment					X		
Patients'acceptability			X		X		
Blindness assessment					X		
Safety assessment			X	X	X	X	X

Abbreviations

CM=Cyclical Mastalgia, VAS-BP=Breast Pain VAS, Nominal Days of Breast Pain=NDBP, WHOQOL-BREF= World Health Organization Quality Of Life Scale-Short Form, QOL= Quality Of Life, MA= Manual Acupuncture, SA= Sham Acupuncture, CRF= Case Report Form

Statistical Analysis Plan

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Statistical Analysis Plan

Statistical methods for primary and secondary outcomes

We will use SPSS 22.0 software(IBM SPSS Statistics; IBM Corp, Somers, NY)to perform all statistical analyses following the intention-to-treat principle. The CI will be established at 95%, and the significance level at 0.05. For continuous data, the data will be presented as mean±standard deviation when normally distributed or presented as median (IQR) when not normally distributed. Statistical comparisons will be performed by the independent-sample t tests or Wilcoxon rank-sum test for continuous data and by X2-test or Fisher exact test for categorical data, as appropriate. A p-value <0.05 will be considered statistically significant.

Informed Consent Form

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Informed Consent Form

Effectiveness of acupuncture for cyclical mastalgia （CM）

Informed consent form • informed notice page

Dear patient:

Your doctor has diagnosed you with cyclical mastalgia. We will invite you to participate in a special research project on health development in the capital. This study is a preliminary evaluation project on the efficacy and safety of acupuncture in alleviating women's periodic breast pain. The topic number is 2022-3-7132. This research scheme has been approved by the Ethics Committee of Beijing Traditional Chinese Medicine Hospital Pinggu Hospital for clinical research.

Before you decide whether to participate in this study, please read the following as carefully as possible. It can help you understand the study and why you want to conduct it, the procedure and duration of the study, and the benefits, risks and discomfort that may be brought to you after participating in the study. If you like, you can also discuss with your relatives and friends, or ask the doctor to explain and help you make a decision.

1、 Research background and purpose

1.1 disease burden and treatment status

70% of women will experience breast pain, and about 2 / 3 of them will suffer from periodic breast pain. Only 22% of them will naturally relieve before menopause, and 57% - 69% of patients will have pain for 2-10 years. Western medicine treatment includes danazol, tamoxifen, bromocriptine, senkoman, night cherry oil, goserelin and non steroidal anti-inflammatory drugs. The above drugs have certain curative effects, and their use is limited due to economic costs, adverse drug reactions, indications, etc. Clinical trials have proved that acupuncture has a definite effect on relieving breast pain. At present, there are some problems in the research on acupuncture treatment of breast pain, such as low research quality, unclear research object and observation index. This study adopts the principle of prospective, randomized control and multi center, takes women with periodic breast pain as the research object, and evaluates the effect of acupuncture in the treatment of cyclical mastalgia from the aspects of reducing the degree of breast pain and improving the quality of life, To explore the mechanism of acupuncture relieving pain and provide a reliable basis for clinical application.

1.2 purpose of this study

To evaluate the clinical efficacy and safety of acupuncture in relieving female cyclical mastalgia.

1.3 study participants and expected number of participants

The participating units include Beijing Traditional Chinese Medicine Hospital Pinggu Hospital (68 cases), Pinggu huangsongyu Community hospital (20 cases) and Pinggu Xiagezhuang Community hospital (20 cases). The total number of cases is expected to be 108.

2、 Who should not participate in the study

① Did not receive relevant treatment in recent 1 month;

② Breast inflammation, breast fibroma, breast cystic hyperplasia and other benign breast lesions;

③ Patients with severe cardiovascular and cerebrovascular diseases or severe impairment of liver and kidney function or coagulation dysfunction;
④ No history of breast cancer in first-degree relatives;
⑤ Costochondritis, chest wall injury, rib fracture and other extramammary pain diseases;
⑥ Patients in pregnancy or lactation;
⑦ Communication barriers;
⑧ Patients with severe mental illness;
⑨ Other researchers are currently participating in the study.

3、 What will you need to do if you participate in the research?

1. Before you are enrolled in the study, the doctor will ask and record your medical history and evaluate the patient's condition. If you meet the inclusion criteria and you voluntarily participate in the study, you will sign the informed consent form. If you are unwilling to participate in the study, it will not lead to prejudice against you or affect your medical care.

2. If you volunteer to participate in the study, you will follow the following steps:

The subjects completed relevant examinations in the outpatient department, and the doctors arranged for the subjects to receive breast color Doppler ultrasound examination. The purpose of this study is to study the clinical data of patients with cyclical mastalgia, including general situation, medical history and breast color Doppler ultrasound. This study is a prospective randomized parallel controlled trial. Subjects who meet the entry conditions are randomly divided into two groups, 54 cases in the experimental group and 54 cases in the control group. Use R statistical software to generate random numbers and groups, and you will be randomly assigned to any one of the two groups. You have a 50% chance of being assigned to each group. Random concealment: a light tight kraft paper envelope is used. The outside of the envelope is marked with the group number, the inside of the envelope is marked with the group, and the envelope is sealed for concealment. Neither the subject, the doctor and the efficacy evaluator can know the distribution scheme of the subject in advance. The experimental group adopted the acupuncture scheme of relieving depression and soothing the liver, and the control group adopted the comfort acupuncture scheme (a special comfort needle; a sterile polyethylene cylindrical foam pad with a bottom diameter of 10mm and a height of 5mm, and the bottom of the foam pad was adhered with double-sided tape to fix the needle on the patient's skin. It felt that there was a similar "needling sensation" of acupuncture into the skin. The evaluation time was: before enrollment, 18 sessions of treatment, and 24 weeks after stopping treatment.

3. Other matters requiring your cooperation

During the course of the research project, new information about the research methods may appear. If there is new information, your study doctor will inform you in time and discuss with you whether you are willing to continue to participate in this study. If you decide to continue participating in the study, you may be required to sign a new informed consent form. The drugs to be prohibited during the study include analgesics related to breast pain, Chinese patent medicine,

etc. Consult your study doctor before taking any new medications. In consideration of your safety and to ensure the effectiveness of the research results, you cannot participate in any other clinical research on drugs and medical devices during the research period.
During the follow-up stage, the doctor may know your situation through telephone, outpatient follow-up, etc.

4、 Possible benefits of participating in the study

If you participate in this study, it is generally treated for 3 times / week, and there will be a certain effect after 2 weeks of treatment. It is possible that your disease condition can be evaluated in time and guide follow-up treatment, but there is no guarantee. You will not receive any form of direct economic benefit from this study.

5、 Possible adverse reactions, risks, discomfort and inconvenience of participating in the study

Your research doctor will monitor the adverse effects of acupuncture. If you have any side effects or discomfort during the trial, it is important that you report it to the study doctor immediately. The research doctor may give you other adverse reactions. If you or your study doctor believes that you cannot tolerate these adverse reactions, acupuncture treatment may be completely stopped and you may withdraw from the study. If you have any discomfort, new changes in your condition or any unexpected circumstances during the study, whether related to the study or not, you should inform your doctor in time, and he / she will make judgment and give appropriate medical treatment.

6、 Related expenses

The cost of continuous acupuncture and color Doppler ultrasound examination of breast before and after treatment were provided by the researchers.
During the study, doctors will do their best to prevent and treat possible injuries caused by this study. If an adverse event occurs in a clinical study, the medical expert committee will determine whether it is related to the study. The sponsor will provide corresponding treatment costs and economic compensation for the damage related to the study in accordance with relevant regulations.

7、 Confidentiality of personal information

Any information and data about you obtained during the research will be kept strictly confidential. Your breast color Doppler ultrasound results will be identified by the study number / number instead of your name. The information that can identify you will not be disclosed to members outside the study group unless you obtain your permission. Any public report on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.
According to medical research ethics, in addition to personal privacy information, research data will be available for public query and sharing. Query and sharing will be limited to network-based electronic database to ensure that no personal privacy information will be disclosed.

8、 How to get more information?

You can ask any question about this study at any time and get the corresponding answer. If there is any important new information during the study that may affect your willingness to continue to participate in the study, your doctor will inform you in time.

9、 You can voluntarily choose to participate in the study and withdraw from the study

Whether to participate in the study depends entirely on your wishes. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect the relationship between you and your doctor, nor will it affect the loss of your medical or other benefits.

For your best interests, the doctor or researcher may discontinue your participation in the study at any time during the study.

10、 What should I do now?

Whether to participate in this study is up to you (and your family).

Before you decide to participate in the study, please ask your doctor as many questions as possible.

Thank you for reading the above materials. If you decide to take part in this study, please tell your doctor and he / she will take care of you

Exclude all matters related to research. Please keep this information.

Informed consent Consent signature page

Name of clinical research project: preliminary evaluation on the efficacy and safety of Jieyu Shujin acupuncture in alleviating female periodic breast pain

Undertaking unit: Beijing Pinggu District Hospital of traditional Chinese Medicine

Project cooperation units: Beijing Traditional Chinese Medicine Hospital Pinggu Hospital
Project assignment:Capital ’ s Funds for Health Improvement and Research(CFH), China No.2022-3-7132
Declaration of consent

I have read the above introduction to this study and have the opportunity to discuss and ask questions with doctors about this study. All my questions were answered satisfactorily.

I know the risks and benefits of participating in this study. I know that participating in the study is voluntary. I confirm that I have had enough time to consider this and understand that:

● I can always ask my doctor for more information.

● I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also know that if I withdraw from the study halfway, especially when I withdraw from the study due to drugs, if I tell the doctor about the change of my condition and complete the corresponding physical and chemical examination, it will be very beneficial to the whole study.

If I need to take any other medication due to the change of my condition, I will consult the doctor in advance or tell the doctor truthfully afterwards.

I agree with the ethics committee of the drug administration or the representative of the sponsor to consult my research data.

I will receive a signed and dated copy of the informed consent form.

Finally, I decided to agree to participate in this study and promised to follow the doctor's advice as much as possible.

Patient's signature: mm / DD / yyyy

contact number:

I confirm that I have explained the details of this trial to the patient, including its rights, possible benefits and risks, and gave him a copy of the signed informed consent.

Signature of doctor: mm / DD / yyyy

Doctor's work telephone: