Study protocol

# Efficacy and safety of acupuncture for chronic pain caused by gonarthrosis: A study protocol of an ongoing multi-centre randomised controlled clinical trial [ISRCTN27450856]

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## Abstract

**Background:** Controlled clinical trials produced contradictory results with respect to a specific analgesic effect of acupuncture. There is a lack of large multi-centre acupuncture trials. The German Acupuncture Trial represents the largest multi-centre study of acupuncture in the treatment of chronic pain caused by gonarthrosis up to now.

**Methods:** 900 patients will be randomised to three treatment arms. One group receives verum acupuncture, the second sham acupuncture, and the third conservative standard therapy. The trial protocol is described with eligibility criteria, detailed information on the treatment definition, blinding, endpoints, safety evaluation, statistical methods, sample size determination, monitoring, legal aspects, and the current status of the trial.

**Discussion:** A critical discussion is given regarding the considerations about standardisation of the acupuncture treatment, the choice of the control group, and the blinding of patients and observers.

## Background

Acupuncture is a traditional Chinese method of medical treatment that uses thin needles to stimulate specific points of the body. Throughout the seventies acupuncture was scientifically studied in many experimental clinical studies. However, controlled clinical trials produced contradictory results with respect to a specific analgesic effect of acupuncture compared to placebos. Based on this experience, a NIH-Consensus-Conference on acupuncture [1] recommended the initiation of further methodologically well designed clinical trials to investigate the therapeutic effects of acupuncture.

In Germany the reimbursement of an acupuncture-treatment has been restricted by decision of the Federal Committee of Physicians and Health Insurance Funds, dating from October 16, 2000. Now, reimbursements of acupuncture are only given for the indications migraine, chronic tension headache, chronic unspecific low back pain, cox- and gonarthrosis when treated within the framework of a so-called model project. It is intended, that the decision for reimbursement of acupuncture will be based on the results of model projects.

The federal association of the AOK and other German health insurance associations agreed to perform such a model project in co-operation with the University of Bochum on a scientific basis to study the quality of health care given by acupuncture treatment. The Universities of Heidelberg, Marburg and Mainz joined this agreement to build four regional trial groups that perform four different randomised clinical trials.

This model project is named German Acupuncture Trials (GERAC) and contains a cohort-study and four randomised controlled trials [2]. The cohort-study collects data on a patient's self-assessment and the physician's assessment of the effect of an acupuncture treatment. Safety aspects are of special interest. Imbedded in the model project are four randomised controlled trials to compare verum acupuncture, sham acupuncture and a standard therapy with respect to efficacy and safety in four relevant indications. These indications are chronic tension headache, migraine, chronic unspecific low back pain [3] and gonarthrosis.

We present the trial protocol of the GERAC-gonarthrosis study with regard to the specific challenges in acupuncture trials. In detail we describe our considerations on the standardisation of the acupuncture treatment, the choice of the control group, and the blinding of patients and observers.

## Methods
The presented study is a multi-centre, randomised, controlled, 3-armed clinical trial conceived as parallel-group design with blinded observation of the primary endpoint via telephone interview. The trial was designed by a steering committee. External information from a scientific advisory board and several clinicians was used to define the acupuncture treatment. The goal of the trial is an assessment of the efficacy with respect to pain and functionality, the patient's condition and safety of a standardised acupuncture in the treatment of chronic pain caused by gonarthrosis in comparison to sham acupuncture and to a conservative standard therapy. Sham acupuncture means needling the patient at defined non-acupuncture points. In this trial we are interested in the specific effect

of needling acupuncture points. Many previous trials using sham acupuncture may have failed because of the difference in the treatment effect might have been too low for the chosen small sample size. Therefore in our study it is planned that about 300 clinical practices include a total of 900 patients, 300 patients for each treatment arm. The investigator of each clinical site must have at least training in acupuncture of 140 hours (A-Diploma) and two years experience in acupuncture. The inclusion and exclusion criteria of the patients are described in table 1.

### Interventions
A standard for *verum acupuncture* was defined to treat gonarthrosis. This treatment is based on recommendations for an optimised acupuncture treatment in clinical studies [4] and based on the most distinguished German textbooks [5-10], as well as from International Studies [11-14]. Furthermore, the therapy was discussed with experts in the field of acupuncture.

The most important and most cited local points in literature were chosen as obligatory points. Therefore the following local points have to be used for every treatment on the affected knee: ST 34, ST 36, Xiyan (Extra 32, including2 needles), SP 9, SP 10 and GB 34. Points of this combination can be omitted only in exceptional cases with documentation, e.g. needling was not tolerated, inflammation or skin injury covering the acupuncture point. In every treatment, the knee and adjoining musculature are examined for further, pressure-sensitive points (Ahshi Points). In addition to the obligatory points, one to four of these Ahshi points per knee may also be treated with acupuncture. These Ahshi points may be equivalent to the following local acupoints: LR 7, LR 8, KI 10, BL 40, GB 33.

A selection of the most important distant points to treat pain in the knee is provided, of which up to two distant points (maximum of four needles) can be chosen for an appropriate therapy in accordance to the individual Chinese syndrome-based diagnosis and the localisation of the cardinal symptom. The use of distant points is not essential. Only the following distant points may be used: LI 4, LI 10, LR 3, ST 44, ST 40, BL 23, BL 60, SP 5, SP 6, KI 3, KI 7, LI 15, SI 10, SI 8, TE 14, LU 6. The choice of distant points should be selected prior to the first acupuncture session. This selection can be changed before starting a new acupuncture session if needed.

Therefore the minimum number of needles is 7 and the maximum is 15. Treatment is performed with sterilised disposable steel needles, 30 × 0.3 mm. The depth of needling should be about 0.5 – 3.5 cm according to the localisation of points [9]. After needle insertion a DEQI has to be tried to trigger in the verum group, followed by a man-

**Table 1: Eligibility criteria**

| Inclusion criteria |
| --- |
| Age above 40 years |
| Member of a Health Insurance Company that participates in the "Model Project" |
| Signed informed consent |
| Chronic pain in at least one knee joint during the last six months as minimum according to the ACR-criteria [26] |
| Radiological signs of a gonarthrosis in the same knee (Kellgren 2 or 3) [27] |
| WOMAC $\geq$ 3 points (on a scale of 0–10) |
| Von Korff Chronic Pain Score $\geq$ 1 |

| Exclusion criteria |
| --- |
| A systemic disease of the musculosceletal system |
| Bone tumour, bone tumour like lesions or metastasis |
| Bone fracture in the lower extremities during the last three months |
| Acute infection or osteonecrosis in the knee joint |
| Surgery of the afflicted extremity during the last six months or planned surgery |
| Radiological signs of a severe gonarthrosis of a Kellgren grade 4 |
| Other pain conditions which compels the patient to take analgesics for more than three days during the last four weeks |
| Addiction to analgesics, opiate or other drugs |
| Acupuncture treatment in the past 12 months |
| Acupuncture treatment of gonarthrosis. |
| Ongoing cortico-steroid therapy or cortisone injections in the past six weeks |
| Dermatological disease within the acupuncture area impairing acupuncture treatment |
| Medical diseases causing an impairment of physical capacity (NYHA > II) |
| Severe Coagulopathy |
| Ischialgia or other neurological diseases |
| History of epilepsy and psychiatric diseases |
| Pregnant or breast-feeding patients |
| Inability to follow instructions (insufficient command of language, dementia) |
| Participation in another clinical study |
| Ongoing legal proceedings concerning pension entitlement |

ual stimulation of the needle, which has to be repeated twice. If both knees are affected, both has to be treated with acupuncture as indicated.

The treatment with *sham acupuncture* was standardised too. To trigger only a minimal unspecific physiological stimulus, sham acupuncture is applied with a minimal depth of needling (not exceeding 5 mm), avoiding real acupoints. A manual stimulation of needles is not allowed. General procedure, anamnesis, diagnostics and communication with patients must be performed exactly as in the verum acupuncture group.

As sham-points ten points in total are chosen, four on each leg and one on each arm. In localising the points, the Chinese measure cun is applied: 1 cun corresponds to the width of a patient's thumb.

• One point between the gall bladder- and stomach-meridian on the distal part of the fibula, 2 cun above the Malleolus lateralis, in the direction towards the knee.

• At each case, one point 2 cun and 6 cun above the Malleolus medialis in the center of the tibia surface area intracutaneous without periost contact, in the direction towards the knee.

• One point in the centre of the thigh on the connecting line from the centre of the patella to spina iliaca anterior superior, in the direction towards the hip.

• One point on the highest spot of the tightened musculus biceps brachii.

Patients randomised to one of the two acupuncture arms get 10 acupuncture treatments within the first six weeks with a duration of needling of 20–30 minutes. Patients in the conservative standard therapy arm should have also 10 visits to try to have the same devotion. Patients graded as "partially successfully treated" during the interview in week 7 are allowed to receive five additional visits/treatments. The criteria is based on a global pain score and not known to the investigator.

All patients treated with acupuncture or sham acupuncture are allowed during the first two weeks of treatment to take Diclofenac (up to 150 mg/day) or Rofecoxib (up to 25 mg/day). During the third treatment week until the end of week 23 of the trial the patient is allowed to use a total dose of 1.000 mg Diclofenac (max. dose 150 mg/day) or a total dose of 175 mg Rofecoxib (max. dose 25 mg/day). During the last three study weeks before measurement of the primary endpoints of the study no further pain medication is allowed. In case of emergency the use of up to 150 mg/day Diclofenac is allowed during the whole duration of the trial, but has to be counted as treatment failure.

The *conservative standard therapy* includes medication up to 150 mg/day Diclofenac or 25 mg/day Rofecoxib according to the need of the patient. The duration of the medical treatment is not restricted, but counted as treatment failure if medication is needed in the last three weeks before measurement of the primary endpoint in week 26.

Each of the three treatment arms are completed by physical therapy (six physical therapy sessions, e.g. isometric training of muscles, walking school, exercises with medical equipment).

All patients may receive orthopaedic modification of shoes and in case of gastrointestinal risk Omeprazol (20 mg/day) or Misoprostol (4 × 200 mg/day). For all patients explicitly excluded during the time of trial are intake of cortico-steroids, non-narcotic analgetics except Diclofenac and Rofecoxib. Also not allowed are injections of any kind, moxibustion, cupping and electro acupuncture.

### Blinding and randomisation
The patients can only be blinded with respect to the acupuncture treatment given. Blinding with respect to the standard therapy is not possible. The investigator cannot be blinded. The WOMAC, the global patient assessment, and the SF12 are measured during a telephone interview performed by a call centre. The person performing the interview is blinded with respect to the therapy of the patient. Patients blindness to the mode of acupuncture is assessed after the last follow up by asking the patient to guess their group assignment. Additionally, patients are asked directly after the intervention phase for the quantity of care they have received during the treatments.

The 1:1:1 block-randomisation, stratified by the trial centre, is performed from an independent centre via fax.

### Endpoints
The primary endpoint is a success rate using a validated German version of the *Western Ontario and McMaster University Osteoarthritis index* (WOMAC) [15,16]. The WOMAC-score (0–100) consists of 24 questions, five of them being related to pain intensity, two to stiffness of the knee and 17 to the functionality of a knee joint. The success is defined as an improvement of at least 36% compared to the baseline measurement before treatment [17] 26 weeks after starting the treatment. If only one knee of the patient is afflicted, the assessment of the WOMAC relates to this knee. If the patient has two afflicted knees, of which only one meets the ACR-criterion and Kellgren 2 or 3, only this knee is considered. In case that both knees are afflicted in accordance to inclusion criteria (ACR and Kellgren 2 or 3), one knee is randomly chosen for the score.

Secondary endpoints: The success rate based on changes of the *WOMAC* from baseline to week 13; the absolute changes in the *WOMAC*-score between baseline measurements and measurements taken in week 13 or 26; the success rate based on the *global patient assessment* in the weeks 7, 13 and 26 (success is defined by rating of 1, 2 or 3 on a 6-point scale); the changes in the eight profiles of the *SF 12* and the relevant summary scores between baseline measurement and the measurements taken in the week 13 and 26; the changes in the *von Korff Chronic Pain Score* [18]. The von Korff Chronic Pain Score will be used to compare pain levels of the four different RCTs of GERAC. Further secondary outcome criteria were number of days unable to work, amount of analgesics taken by the patients, number of adverse and severe adverse events.

All efficacy parameter are taken during telephone interviews performed by a call centre (Table 2).

**Table 2: Time schedule for each patient**

| Week | Action |
|------|--------|
| -2 | Screening |
| -1 | Telephone interview, baseline |
| 0 | Randomization |
| 0–6 | Treatment |
| 7 | Telephone interview, endpoints |
| 7–13 | Where applicable: treatment prolongation |
| 13 | Telephone interview, endpoints |
| 26 | Follow-up visit and telephone interview, endpoints |

### Safety evaluation
In each visit, the investigator has to ask a patient if he or she has suffered adverse events since the last visit. Analysis of safety data is performed with respect to frequency of adverse events as a whole, of adverse events in the three different therapy groups, of adverse events stratified with respect to severity, of serious adverse events, of adverse

events stratified by aetiology, and of adverse events stratified by system organ classes (MedDRA).

### Statistical analyses

Statistical methods are used to assess the quality of data, homogeneity of treatment groups and the assessment of efficacy and safety of treatments given. The analysis is performed on the basis of an intention to treat (ITT) population and with respect to ITT principles. A patient belongs to the ITT population if at least one treatment has been carried out after the randomisation and the patient participated on at least one treatment session. The primary endpoint will also be analysed on the basis of a "per protocol" population.

To compare the three treatment arms multiple testing is performed according to the closed test procedure. First the global test of WOMAC-criteria will be performed. If the global test of WOMAC-criteria is non-significant then no further testing will be performed. If it is significant, all two-group comparisons will be tested. This procedure guarantees the overall alpha error of 5% even if all single statistical tests are performed on the 5%-level.

As a statistical model a logistic regression on individual (not marginal) changes is used to interpret the individual odds ratios (likelihood-ratio test). The model incorporates centre and number of treated knee joints as stratification variables. In cases of low rates of recruiting in individual centres, the patients will be combined into larger units using a nearest-neighbourhood procedure.

In case of the necessity for an interpretation of results in the sense of a non-inferiority, a confidence interval approach will be used. As the non-inferiority margin for the odds ratio 0.4 will be used, derived with parametric bootstrap based on 8 points as non-inferiority margin on the WOMAC (0–100) scale [19].

The statistical analyses of the secondary endpoints have explorative character. A univariate analysis with respect to the different treatments will be performed for the dichotomised as well as an ordinal WOMAC-measurement in week 6, 13 and 26. Both dimensions calculated from the SF12 measurements will be presented graphically for every treatment group in week 6, 13 and 26. This allows a comparison between the treatment groups but also the observation how the health status may change in the course of time. The global patient assessment will be analysed as ordinal as well as dichotomised (1–3 defined as success) variable.

### Sample size

In sample size calculation, we slightly modified the approach of Farrar [20] regarding the effect of the verum acupuncture. For the primary endpoint, the following assumptions are made: Success rate standard therapy 40%, sham acupuncture 50%, verum acupuncture 60%, 30% dropout (a dropout is counted as failure). This modifies the success rates to 28%, 35%, 42%. To detect a significant difference on a global alpha error of 5% with a power of 90% between these three groups of therapy, 294 patients per group are required for this scenario (nQuery Advisor V 1.0, based on Formula 5 from [21]).

The confirmative analysis uses a logistic regression with likelihood-ratio test instead of a $Chi^2$-test. Via simulation it can be shown that the power of the likelihood-ratio test is 91%. Also the use of covariates means a slight gain of power [22].

### Monitoring

The aims of the monitoring consist of making sure that the rights and the welfare of all participants in this study are ensured in the clinical sites as well as having high quality data. This is granted by observing the compliance with the study protocol, the GCP-guidelines and legal regulations by five external monitoring centres. To increase the compliance with the trial protocol and the quality of data each investigator had to attend one instruction course before starting the recruitment of patients. Here detailed information was given to the trial protocol, the case report forms and the verum and sham acupuncture technique. Furthermore, to assure the quality of data, entries in the CRF are checked according to completeness, correctness and comprehension during four monitoring visits in each centre. Queries for discrepancies are generated in Heidelberg and must be solved. For all study participants the examination of basic facts should be completely reported, i.e. existing patient, patient number and initials, the availability of written informed consent, serious adverse events and their correct report. For 10% of the study participants all entries which are relevant for the efficacy and safety analysis will be verified completely.

Additionally the monitor observes the progress of recruiting patients in each study centre and if necessary the participating physician will be reminded of the study by a telephone call. Finally each investigator can demand for the help of a study nurse if there are any problems with the documentation of the first patients.

### Ethical and legal aspects

The study is conducted according to the Declaration of Helsinki, the Good Clinical Practice (ICH-E6), and the German laws. Patients are included after information about the study and signing the informed consent. The trial protocol was approved by the Independent Ethics Committee (IEC) of the medical faculty at Heidelberg, as well as by the IECs responsible for the clinical sites. A

patient's insurance was effected in order to cover risks connected directly with the study.

### Current status of the trial

Recruitment of patients was started in November 2001. But it took about one year having a proper recruitment rate. It is intended to include patients until March 2004. The follow-up ends in autumn 2004. Currently 300 clinical sites are involved in the study.

## Discussion

Publishing information about ongoing trials is quite uncommon until now. Report of a trial with no results seemed to make no sense. Why should we provide information about ongoing trials? Mainly three issues justify the publication of protocols:

Detailed information about ongoing trials can give helpful information about research activities, treatment definitions, design of the trial, endpoints and statistical procedures. Beyond new clinical trials also systematic reviews are of interest. Published methods can reduce publication bias because publishing results even if they are negative is obligatory. Additionally the reviewer is able to look for published protocols and study registers to investigate the publication bias [23]. Due to the same intention of registers we added the trial to the current controlled trials register http://www.controlled-trials.com. A further topic is the quality of analyses and interpretations of clinical trials. For the interpretation of clinical trial results it is necessary to know whether the analysis was planned or only post hoc. A published study protocol can simply be compared to the results of the trial. Therefore planned and post hoc analyses are distinguished very carefully in the presentation of the results.

GERAC is currently the largest randomised clinical trial in acupuncture on patients with chronic pain due to gonarthrosis. We tried to design the trial as good as possible but all trials, especially acupuncture trials, have their advantages and disadvantages regarding blinding, treatment, and investigators:

Blinding in acupuncture trials as one method to reduce bias is difficult. But we include only patients without acupuncture experience for gonarthrosis and have blinded assessment of endpoints. The advantage of the telephone interview is that the assessor has less influence to answers of the patients than in an face to face interview. Also the patient is able to stay in his habitual environment and may be prepared by receiving the questionnaire before.

The comparator of the verum acupuncture is a sham acupuncture and we are aware that each needle stimulation might have physiological effects and therefore sham acupuncture is not a real placebo. We deliberately do not use the placebo needle which does not penetrate the skin [24]. Using the placebo needle one is able to detect *any* effect of needling. But sham acupuncture as control group matches with our study aim to investigate whether the effect depends on the acupuncture points or not.

We are aware that one disadvantage of this study might be the exclusion of moxibustion and ear acupuncture. But the aim is to investigate body acupuncture. Furthermore blinding with moxibustion is not possible. Therefore we do not know how much this might influence the effect of acupuncture. However, we investigate a standardised acupuncture even if some practitioners will disagree with our choice of acupoints. But the advantage of standardisation is to receive reliable results. If negative or positive, they only count for this special standardised treatment. Further, we do not exactly know which is the optimal number of acupuncture treatments. According to a consensus of leading acupuncture experts we decided to treat ten times with the possibility of a further five treatments if the patient's condition does improve somewhat, but not sufficiently.

Performing the trial as a multi-centre pragmatic trial on outpatients seems to provide us with an estimation of realistic effects. But one criticism might be that too many treatment sites were included. Too many investigators might influence the results in different ways. Therefore the therapy is standardised, all investigators have to have at least the A-Diploma and 2 years experience of practising acupuncture, the statistical analysis adjusts for the investigator heterogeneity, and the quality of data is improved by extensive monitoring and the query process.

Actually there is a second model project (*ART* = Acupuncture randomised trials) in Germany including also a trial about acupuncture and gonarthrosis [25]. The design of GERAC and ART is different, which provides complementary information. The results of the gonarthrosis trials will be comparable due to the use of the WOMAC-Score as primary endpoint. Both trials compare a standardised acupuncture treatment with sham acupuncture, but the third group is different: No further treatment is given in the ART trial (waiting list) and a medical treatment is given in the GERAC trial. In the interpretation of the results it has to be considered that assessment of the primary endpoint in GERAC is in the 26th week after begin of the treatment, while in ART it is in the 8th week. GERAC emphasises the long term effect and therefore included a higher number of patients. It must be taken into consideration that the results of each trial are only valid for the specific defined acupuncture therapy. E.g. the ART trial allows ear acupuncture whereas GERAC does not. A positive result for the acupuncture treatment does not automatically signify

the best possible treatment. Another scheme of acupuncture might as well lead to better (or worse) results. A negative result of this acupuncture treatment does not imply that there is no other treatment of acupuncture with a better effectiveness.

## Competing interests
None declared.

## Authors' contributions
KS is a specialist in acupuncture. He was responsible for the standardisation of the acupuncture therapy and is the main author of this paper together with SW who is biometrician and project manager. UM is the responsible biometrician of the project. CK is responsible for the site management. JK and HPS are specialists in orthopaedics. KS, JK, HPS, NV are members of the steering committee. The whole team gave comments on the drafts for this paper.

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