

Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding

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SUMMARY. Evidence of effectiveness is increasingly used to determine which health technologies are incorporated into public health provision. Acupuncture is a popular therapy that has been shown to be superior to placebo in the treatment of nausea and dental pain, and promising for migraine and osteoarthritis of the knee. For many other conditions, such as chronic pain, in which acupuncture is often used, the evidence is either insufficient or negative. Misleading results may occur for a number of reasons. False negative results may arise from inadequate treatment schedules and inappropriate control interventions. This consensus document considers these issues with the aim of improving the design of efficacy trials of acupuncture in order that they are more likely to be conclusive and more meaningfully interpreted.

Clinical trials of acupuncture must use an optimal form of treatment; this can be defined by examining standard texts, by surveying and consulting experts. There are a great many variables in treatment (such as point selection, form of stimulation) all of which need to be addressed in designing and reporting clinical trials. The control procedure is determined by the precise research question that is being addressed. For efficacy studies, in which the question is whether acupuncture has specific effects (i.e. is superior to placebo), sham forms of acupuncture appear the most appropriate method of controlling for needle penetration. A recent development of blunted, telescopic needles may represent a major advance. Such procedures may produce a therapeutic response so should preferably be recorded as 'sham' procedures rather than true 'placebo' controls. Blinding in clinical trials is an accepted means of reducing bias. Patient blinding in acupuncture studies can be achieved by sham procedures and its success should be measured. While practitioner blinding is difficult, though not impossible, blinding of the observer and the analyst should be considered as the ideal for all studies. A number of recommendations are made which aim to improve the quality of sham-controlled acupuncture studies. © 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

It is increasingly recognised that decisions on the type of health care that should be provided must be made on the strength of the evidence for effectiveness, safety and cost-effectiveness. This applies both to newly introduced technologies, and, perhaps less obviously, to existing but unproven therapies such as acupuncture. This paper is concerned with studies that investigate the efficacy or thera-

peutic effectiveness of acupuncture, not safety or cost-effectiveness.

The current evidence for the efficacy of acupuncture may be summarized as follows: a systematic review found it to have an anti-emetic effect that was superior to various controls, including placebo controls, for treating nausea of three different causes (pregnancy, surgery, chemotherapy).¹ Subsequently, the authors of a meta-analysis found acupuncture to be superior

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to placebo, and similar in efficacy to anti-emetic drugs, in preventing early postoperative nausea and vomiting.² The evidence from the systematic review had suggested that acupuncture reduced chemotherapy-induced nausea and vomiting; this has been supported by a subsequent high-quality study.³ The evidence from other systematic reviews of acupuncture is promising for a few indications, such as fibromyalgia,⁴ but in most cases is still insufficient to draw firm conclusions. The current review evidence is inconclusive for asthma⁵ and for tinnitus,⁶ and is negative for smoking cessation⁷ and for weight loss.⁸

Turning to systematic reviews of the effect of acupuncture in the treatment of pain, a review of its effect on acute dental pain was positive,⁹ and it appears that electroacupuncture, though not manual acupuncture, is more effective than placebo in reducing experimental pain.¹⁰ Results are promising but not conclusive for treatment of both knee osteoarthritis¹¹ and migraine.¹² Reviews of acupuncture for the treatment of a heterogeneous range of common painful conditions are generally negative, including chronic pain,^{13,14} and neck pain.¹⁵ For back pain, results of reviews have been discordant.^{16–18} Reviewers frequently comment that the quality of acupuncture studies is generally not high.

In summary, the rigorous evidence for the efficacy of acupuncture is surprisingly negative when compared with its positive image in the minds of the public and the acupuncture profession. Two interpretations can be made: either acupuncture is a good placebo and nothing more; or the negative results are false. False negative results can occur for several reasons, including chance, inadequate sample size, poor choice of outcome measures (either not valid or not sensitive), inadequate treatment, or inappropriate control procedure used (e.g. it may have some therapeutic effect).¹⁹ This paper discusses aspects of the last two factors, i.e. inadequate acupuncture, and choice of appropriate control, together with blinding, with a view to making recommendations that will improve the design of future studies. It aims to draw mainly on empirical data from readily accessible reports of research in humans.

OPTIMALLY EFFECTIVE ACUPUNCTURE

Acupuncture is notable for the amount of variation that exists in every aspect of its use. There are fundamentally different perspectives about whether the therapy should be understood from an 'energetic' or 'neurophysiological' basis. Interventions used in some previous studies have not reflected clinical practice that would be acceptable to many acupuncturists, which seriously limits the conclusions that can be drawn (for example^{20,21}).

The ideal way to establish optimally effective acupuncture would be by controlled comparative studies looking at every relevant variable of treatment. These have been informally reviewed.²² Such studies would probably need to be clinical trials rather than laboratory experiments, since no objective physiological marker for clinical effectiveness of acupuncture has yet been identified. Alternative methods of establishing optimally effective acupuncture have been suggested: these include textbook review²³ or surveying and consulting experts to establish a consensus.^{24,25} The use of large scale outcome studies comparing different acupuncture methods may be limited by other differences between the groups, such as different practitioners. An established acupuncture school that teaches a consistent treatment approach could provide a standardised (and therefore replicable) treatment protocol for clinical trials. Treatment variables that should be considered are listed.

Acupuncture points

There seem to be two fundamental practical questions about acupuncture points, apart from the question of whether and how they differ anatomically and physiologically from non-points. The first is whether practitioners can locate them consistently. One investigation suggested that newly trained acupuncture practitioners were unreliable in locating points LI10 and ST40.²⁶ The second question is whether needling acupuncture points is more effective than needling other sites, either sites that are known acupuncture points or non-point non-meridian sites. Hypothetically, any acupuncture effect might diminish with increasing distance from the point. Few studies have compared the effects of needling acupuncture points with precisely similar stimulation given at non-point, non-meridian, non-tender sites. Clinical experience suggests that acupuncture can be effective when the needle is inserted anywhere in the appropriate segment²⁷ or at motor points.²⁸ It has also been surmised that accurate point location is necessary for treating some indications, such as the treatment of nausea,¹ but not for others, such as smoking cessation.²⁹

Needle design

Needles vary not only in length (see depth of insertion, below) but in gauge and in surface finish, which may be unpolished, polished, or coated in a substance such as silicone oil to assist insertion. In a theoretical discussion accompanying experimental work, Marcus pointed out that the volume of tissue damage increases with the square of the needle radius.³⁰ Using the skin flare response as an indicator of strength of stimulation, he proposed and provided some validation for a 'Unit of Acupuncture treatment' that is determined by needle

radius and length, and a constant that reflects stimulation.

Depth of needling

The optimal depth of needle insertion is unknown. It may differ depending on the condition, age, and body weight. For example a myofascial trigger point might only be inactivated if the needle penetrates it. Deep needling was superior to shallow needling three months after the end of treatment for lumbar pain, but not immediately after.³¹ In a small RCT in children with migraine, subdermal needling had a significantly greater effect on migraine frequency and intensity, as well as on opioid peptide release, than intradermal needling at the same sites.³²

Duration of needling

There are few comparative studies that investigate the optimal duration of needling. In a study in patients with chronic head or neck pain, more patients responded after 30 or 60 minutes treatment than after 1 or 5 minutes.³³ The results after 15 minutes were intermediate. Short, 5 minute treatments produced the same outcome as 20 minute treatment in patients with neck and shoulder pain,³⁴ although the study was small and the authors pointed out other limitations. Theoretical considerations include the duration of stimulation that is needed to release opioid peptides or other transmitters.³⁵

Number of points used

Again, there appears to be little empirical evidence whether treatment requires a particular number of points to be treated in order to be considered adequate. A textbook review concluded that the use of at least eight points was optimal for treatment of osteoarthritis of the knee, but the studies included in the review did not produce evidence to support this conclusion.¹¹

Stimulation

Needles may be stimulated by hand, by warmth (moxibustion), or by electric current. In a laboratory study, Marcus found that the duration of manual stimulation contributed much more to the strength of acupuncture than the depth or gauge of the needle.³⁰ Patients with chronic sinus pain were more likely to gain relief from deep needling with stimulation eliciting deqi than from shallow needling without stimulation.³³ Patients with back pain who selected low frequency electrical stimulation gained longer duration of relief than those who preferred manual or high frequency electrical stimulation.³⁶ There are few hard data with which to make informed decisions about strength, duration and repetition of stimulation for opti-

mal effect. It is interesting to note the variety in methods of needle stimulation in different periods of history and parts of the world, from the lightest, non-invasive (Toyo Hari) or subcutaneous needling currently used in Japan, to the vigorous stimulation used in some parts of China.

There is a similar lack of consensus on whether needle sensation (deqi) is necessary to produce a therapeutic effect. Many practitioners believe it is essential for achieving therapeutic success, P Chin (personal communication) found that success was higher in patients who reported feeling deqi, and there is support from physiological and clinical trials.³³ However, several treatment traditions (e.g. Japanese) use little or no needle sensation. Few studies have compared just needling with and without sensation (most studies compare different points). Needle sensation may not be a single phenomenon,³⁸ and it may differ between points.³⁸ It may depend on the innervation of the tissue being needled, whether subcutaneous tissue, fascia, muscle or periosteum. For inactivating trigger points it seems that a twitch response may be the key factor,³⁹ but it is not known whether there are any physiological parallels between needle sensation and the twitch response.

Point selection

Each acupuncturist has his/her own individualized treatment styles based on clinical experience and personal belief. Many practitioners believe it is vital to use treatment that is individualized to the patient, involving for example, choice of points, or method of stimulation. The importance of individualization in comparison with formula acupuncture has not been demonstrated in clinical trials. Individualization may be applied at various levels, including 'algorithmic' (e.g. treating meridians according to the referral of back pain³⁶ or according to some principle such as Five Element diagnosis or myofascial trigger points), or totally personal including adopting a particular emotional approach. In practice, practitioners tend to use certain patterns of points on all or most of their patients.⁴⁰ Treatment protocols should reflect the best practice of a particular 'school' as this could be replicable.

Number and frequency of sessions

A textbook review found that an average of 10 treatments (range 7 to 15) is important in achieving positive results in treatment of osteoarthritis of the knee.¹¹ In a chronic pain review,¹⁴ studies in which patients received more than six sessions were significantly more likely to be positive than those with fewer sessions. The acupuncture skin temperature response is more marked after eight sessions of acupuncture treatment.⁴¹ One study suggested that acupuncture was more successful when given weekly than twice weekly.²²

CONTROL PROCEDURE

Purpose of control group

Many case series and uncontrolled trials of acupuncture have been published in which the majority of patients have improved over the treatment period. Such improvement may be due to a number of factors not associated specifically with acupuncture, including chance, the natural history of the condition, regression to the mean, the therapeutic relationship, or even an apparent effect simply from measuring patients in an experimental context (Hawthorne effect). It may also be due to some other aspect of the acupuncture treatment, including the effects of:

1. The acupuncture consultation
2. Patients' beliefs about, attitude towards and expectations of needling and acupuncture
3. Practitioners' expectations of acupuncture
4. General physiological effects of needle insertion
5. The (putative) effects of appropriate acupuncture needle stimulation at the correct location.

The last item is usually called the 'specific' effect in contrast to the other 'non-specific' effects, although some effects that are included in the term 'non-specific' may be peculiar to acupuncture (e.g. the specific expectations of the effects of needling compared to laser stimulation). The contribution of each component to the overall effect has often been assumed to be additive; however, it is theoretically possible that some non-specific factors, such as therapeutic relationship, may be necessary to amplify the physical effect of the needle, or even to facilitate it.

Control groups are used in order to test the degree to which each particular component (or group of components) of the intervention contributes to the total therapeutic effect. The changes common to the control and treatment groups can be assumed to be equal, provided that there is no systematic difference between them in known or unknown predictive factors (which is the aim of randomization). Therefore, any differences between the outcome in the groups can be attributed to the difference in interventions between the groups.

Choice of control procedure

The research question determines the choice of control. If the question is whether acupuncture is better than doing nothing, then the control group receives nothing, e.g. waiting list. If the question is whether acupuncture is better than current best treatment for the condition, then the control group must receive current best treatment. If the question is whether acupuncture needles have any specific effect, then the control group must receive some

procedure that is indistinguishable from the true acupuncture intervention. The remainder of this discussion applies, for the most part, to the third situation.

Acupuncture 'placebo' controls

In the context of controlled trials, a 'placebo' can be defined as an inert treatment that elicits the knowledge or belief in participants that they have received an intervention (the placebo effect), and that is not distinguishable from real treatment. Some would argue that it may be enough for the placebo control to be as credible as real treatment. Using placebo controls in clinical trials is not ethical under all circumstances, for example if patients are denied access to an available, effective therapy. This discussion presupposes ethical criteria are met.

Importantly, placebos can control for three different aspects of acupuncture treatment:

1. The effect of needle stimulation, in which case the placebos need to be applied at the correct sites
2. The effect of acupuncture points in general, in which case they should be applied off-site and off-meridian
3. The effect of the specific acupuncture points for a patient or condition, in which case they need to be applied at irrelevant acupuncture points.

Terminology: 'sham' or 'placebo'?

The question of whether any device used as a control can be a truly inactive 'placebo' is a matter of discussion. Penetration, or even pressure, on the skin can cause a physiological response and so might not always be inactive.⁴⁶ The terminology for reporting acupuncture control interventions has not been standardized. Lewith and Machin used the term 'sham' acupuncture to mean needling wrong points and 'minimal' acupuncture to mean needling superficially,^{64,65} whereas Hammerschlag used the word 'sham' for any invasive but inappropriate procedure.⁶⁶ This forum recommends that the terms 'penetrating sham' (or 'invasive' sham) and 'non-penetrating sham' (or 'non-invasive sham') should be used for all procedures that are designed to seem like acupuncture, but are not genuine. This terminology reflects the distinction between trials of drugs (which use placebos) and trials of procedures such as surgery (which use sham treatment). This forum also recommends that study reports should describe precise details of the apparatus, the procedure, the site and the regime used in the study, using the STRICTA guidelines (Standards for Reporting Interventions in Controlled Trials of Acupuncture) in addition to the usual CONSORT guidelines.⁶⁸

The research question addressed by placebo studies

Placebo controlled trials investigate whether acupuncture needles have specific effects beyond placebo. Acupuncture is commonly dismissed as 'only a placebo'; this accusation can only be refuted with placebo controlled trials. In addition, some consider that evidence for efficacy beyond placebo is necessary before acupuncture could be adopted by the UK's national health service.^{42,43} Naturally, placebo controlled trials do not address the question of whether acupuncture is more effective than other treatments, or whether it is cost effective.

If acupuncture can be established to be superior to placebo in a certain number of conditions, it might be considered to have been shown to be 'credible'. Placebo controlled trials will then not be necessary for other similar conditions and studies can then concentrate on direct comparison with other treatment options. It seems sensible to aim at accumulating this type of trial in those clinical areas where trials already exist and acupuncture appears to have a good effect, such as nausea, migraine, osteoarthritis of the knee, addiction, fibromyalgia, musculoskeletal pain and myofascial pain.

Some 'sham acupuncture' procedures

Some early trials in the west compared genuine acupuncture with needle insertion, with stimulation, either into inappropriate points⁴⁴ or into sites outside traditional points or meridians.⁴⁵ These studies were designed to compare the effects with stimulation at appropriate points, but the control procedures themselves seem likely to have physiological effects.⁴⁶ In addition, there is disagreement about which points are inappropriate: one review⁴⁷ found that control points used in some asthma studies were inappropriate because in some systems of acupuncture they are said to be effective in changing lung function. Another commonly used 'sham' control procedure is the insertion of needles superficially without manipulation at inappropriate sites.⁴⁸ Again, it is recognised that this control intervention may produce physiological stimulation.²⁹ It should be noted that the outcome of all controlled studies may be profoundly affected by the information patients are given, both in writing and orally.

Acupuncture has also been compared with other 'placebo' interventions such as mock TENS,^{49,50} placebo tablets,⁵¹ or with inactivated laser apparatus.⁵² Their credibility has been tested,⁵² but until they are shown to have the same total psychological impact as acupuncture we believe that these control procedures may not be directly comparable.⁵³ Any differences between the effects of these controls and genuine acupuncture

could, at least theoretically, be due to differences in placebo effects.

Several different and imaginative methods have been used to give the impression of penetration by a needle. Some authors have not used a needle at all, but substituted a finger-nail,⁵⁴ guide tube⁵⁵ or cocktail stick.⁵⁶ Others have used a normal needle but in an abnormal way, either just pricking the skin⁵⁷ or not penetrating the skin but becoming embedded in a plastic plug at the end of the guide tube,⁵⁸ or pressing the skin with the blunt end of the needle.⁵⁹ Recently, a blunted needle was used,⁶⁰ first inserted through a supporting sterile foam block then pressed on the skin. The foam block compresses to give the impression that the needle is penetrating the skin.

Telescopic needles as 'placebo'

A telescopic needle has been devised as a control: this has a blunted tip, and the shaft has been detached from the handle so that the handle slides over the shaft when the needle is pressed, giving it the appearance of penetrating the skin.⁶¹ A validation study found that far fewer volunteers felt a dull sensation (equated with needle sensation, *deqi*) with the placebo needle, compared with the real needle. In a clinical trial, true needling was found to be superior to this sham needle in the treatment of shoulder injury.⁶² This suggests that actual penetration of the skin is an important component of acupuncture treatment. Further studies are warranted to confirm whether the new needle can be used at 'correct' points without producing a clinical effect. It appears to offer a breakthrough in placebo needle design, although there are still practical difficulties using the device, the procedure is somewhat artificial and adequate needle manipulation may be difficult.

In order to allow retention of the needle during treatment, the needle was supported by an adhesive dressing applied over an O ring. A variation on this method is a base unit designed to hold the guide tube and needle.⁶³ Validation studies in progress suggest that the needle does not induce *deqi*, supporting the earlier finding.⁶¹

Point selection for sham control procedure

Selecting the control location should be done with care. While many acupuncturists believe that stimulating defined acupuncture points influences *qi*, others argue that any effects of acupuncture are due to the stimulation of nerve endings, which can occur at many sites. It is not possible at present to resolve these two approaches, because of lack of evidence. It seems sensible to recommend that research done according to each theory should acknowledge the beliefs of the other. Thus, traditional acupuncturists should choose control points

that are both not appropriate for the condition and not in the affected segment (if relevant). Similarly, those using the theory of nerve stimulation should choose control points that are both in different segments and are not on points or meridians. In addition, the sensation generated should be kept to a minimum and should be recorded.

Some other problems arise in attempting to measure the specific effects of acupuncture. One is that specific effects may be small in relation to acupuncture's apparently powerful placebo effects.⁵⁸ Another difficulty is in differentiating the effects of acupuncture from the placebo response: the analgesic effects of both (at least, in acute pain) appear to be partly mediated by endogenous opioids.^{35,69}

BLINDING

Blinding any individual who participates at any stage of a trial reduces the risk that his or her judgement is biased by preconceived opinions. In the context of a sham-controlled trial, a second aim of blinding is also to allow the specific effects of treatment to be measured. Six roles in a study can theoretically be blinded (masked), though several roles may be undertaken by one participant.

Patient blinding

Blinding patients involves using a sham procedure (discussed above) and ensuring that the blinding is maintained by the information they receive from verbal or non-verbal communication. For the following discussion it is assumed that participants are acupuncture naïve, so their expectations of the acupuncture procedure are not influenced by previous experience.

The patient information leaflet (in US, Patient Consent Form) for each study needs to be written carefully as it needs to balance the patients' rights to safeguard their integrity with the researcher's need to limit patients' knowledge in order to maintain blinding. Attitudes and opinions of Research Ethics Committees (in the US, Institutional Review Boards) are not standardized and it may be important to discuss the precise wording with the committee chairman. The particular problems that arise in providing information for patients in acupuncture trials are considerable, and are currently being discussed by the International Acupuncture Research Forum.

It is usual to standardize and minimize therapist/participant interaction in order to reduce practitioner bias.⁷⁰ A variation of minimal interaction permits therapists to give standardised, predefined answers to certain frequently asked questions.⁶² However, investigators should recognise that participants can also infer their group allocation from the 'body language' of the therapists. For example, it may be necessary to standardise the performance

of real and 'placebo' procedures, to make sure, for example, that the therapists have equal confidence in locating real and sham acupuncture points.⁷¹ A possible weakness of standardised interaction is that specifically avoiding a therapeutic relationship might diminish the effect of the treatment.

Acupuncturist blinding

It is not easy to blind practitioners in trials of manual treatments like acupuncture. Previous attempts have included training a novice specifically for the study.⁷² This is, in general, not satisfactory, since the quality of treatment is inevitably less than optimal. Another method has been to arrange that the acupuncturist treating the patient is blinded to the diagnosis. This has been achieved by stating one of two alternative diagnoses⁴⁴ or by providing one of two treatment protocols, only one of which is appropriate.⁷³ If using a formula treatment, an 'irrelevant' formula should be established by consensus beforehand. For individualised treatment, the decision of the acupuncturist who makes the diagnosis should ideally be subject to consensus. Further studies are needed to evaluate these methods.

Assessor blinding

All assessors should be blinded in order to reduce measurement bias. The blinded assessor may be the blinded patient or a member of the research team. Assessment might only be regarded as truly blinded if the data are coded and entered into computer by blinded personnel.

Analyst blinding

Though less commonly used, this rigorous step ensures that the statisticians who perform the analysis should be unaware of which group received active treatment until they have finally determined whether there is a significant difference between the groups.

Other participants

Usually, the therapist who provides other care for the patient included in a study remains blinded to the group allocation. Masking of the investigator who is responsible for writing the report (at least, up to the end of the results section) can be considered but is probably not commonly arranged.

Testing the success of blinding

In all blinded studies, the success of masking should be measured. This should be performed early in treatment to avoid being influenced by the outcome of treatment. Two ways are commonly used in acupuncture studies. The first operates as a surrogate for testing blinding, and tests for psychological impact of the two interventions. The credibility of the interventions is assessed by four specific questions, such as whether the participant would recommend the treatment to a friend.⁷⁴

In the second method, patients are asked the direct question whether they believe they were in the real or sham groups (or whatever terminology is appropriate for the original patient information leaflet).⁵⁵ Both methods have their drawbacks. In particular, the analysis is problematic: some acupuncture studies have tested for statistical differences between the credibility of the two treatments. If there are not statistical differences, they conclude that the treatments are equally credible, or 'equivalent'. However, showing that two groups are equivalent is very different from showing that they are not different: different sample size calculations and methods of statistical analysis are required, and statistical specialists should be consulted.

RECOMMENDATIONS FOR ACUPUNCTURE CLINICAL TRIAL DESIGN BASED ON CURRENT EVIDENCE

General points: CONSORT and STRICTA guidelines should be followed closely in designing and reporting studies. Treatment and control procedures must be carefully described so that the correct conclusions can be drawn and the procedure can be replicated. Most successful studies involve collaboration between methodologists (researchers), statisticians and practising acupuncturists in design, performance and analysis.

1. Explicit effort should be made to establish the optimally effective acupuncture for the condition. Treatment protocols should be defined by either:
 - Empirical research exploring each question in logical order
 - Textbook survey
 - Survey and consensus of experienced practitioners
 - A combination of these methods.
2. The research question determines what control or comparison procedure should be used.
3. The following factors should be defined for the treatment and control schedules, and reported: acupuncture style, rationale for point selection, location of points used and number of insertions, depth of insertion, responses elicited, needle stimulation and retention time, type of needle, number and frequency of sessions, other treatments given, the rationale for selection of control intervention and information given to patients.
4. Consideration should be given to nature and location of the control. To test the effect of point-specificity, the control may be usual stimulation at either points that are agreed to be inactive for the condition, or non-point,

non-meridian, non-segmental sites. To test the effect of needle stimulation, an inactive procedure at the correct site represents the ideal.

5. Studies investigating the effects of needle stimulation should consider using 'sham acupuncture' controls; the impact of other non-needling placebo procedures may be different.
6. The term 'sham' is preferred to 'placebo', since known control procedures may not be inactive. Control procedures can usefully be described as 'penetrating sham' or 'non-penetrating sham'.
7. A novel sham intervention uses a blunted needle in which the shaft is separate from the handle; the latter is therefore free to slide over the shaft, mimicking penetration. It is a promising development that warrants further investigation.
8. Assessor blinding should be regarded as essential in principle.
9. In sham-controlled studies, patient blinding should be preserved by careful attention to verbal and non-verbal communication.
10. Success of patient blinding should be assessed, preferably early in the study. The analysis of credibility assessment requires particular attention.
11. Practitioner blinding for acupuncture studies is possible but involves elaborate methods so is unlikely to be routinely incorporated in studies.

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