The Context and Meaning of Placebos for Complementary Medicine

George Lewith1, Fiona Barlow1, Caroline Eyres1, Andrew Flower2, Sue Hall3, Val Hopwood4
1 Primary Medical Care, University of Southampton,
2 Department of Primary Care, University of Southampton, UK
3 School of Health Sciences, University of Southampton, UK
4 Department of Primary Care, Southampton, UK

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Summary
Calls for placebo-controlled randomised trials in complementary and alternative medicine (CAM) are entirely reasonable. However, they present major methodological problems, particularly when we understand so little about the underlying biological mechanisms involved for many of these therapies. Designing a placebo in CAM is frequently dependent on untested assumptions about the specificity of a particular CAM intervention. In this paper we address the development and application of placebos to clinical trials of homeopathy, acupuncture, kinesiology, Chinese herbal medicine and healing. Each therapy-based vignette is authored by a researcher from the Complementary and Integrated Medicine Research Unit at the University of Southampton who has specific expertise in the field. The essential research question within this review is: can we legitimately claim to have placebos for these particular CAM interventions? In some areas of CAM the debate has become very involved and sophisticated, for instance in acupuncture but for other areas, such as healing, our understanding of placebos is currently limited and very naive. For instance, if acupuncture is not part specific, then many so-called 'placebo-controlled' acupuncture trials are both misconceived and misleading. We have addressed this debate in what we hope is a thoughtful and rigorous manner with a view to developing realistic, reliable and credible placebos for randomised controlled studies when and where possible. However, our conclusions suggest that we are some way from developing valid, credible and reliable placebos for most CAM therapies.

Schlüsselwörter
Alternativemedizin - Placebo - Randomisierte kontrollierte Studie

Zusammenfassung
Introduction

The placebo has been conventionally conceptualised as an inert agent or procedure that lacks therapeutic effects through the induction of a variety of psychological mechanisms, including expectation of clinical improvement and Pavlovian conditioning that both trigger self-healing [1]. In the late 1970s, the demonstration of a measurable opioid response [2] confirmed that the effect of placebo is a real physiological process, rather than 'all in the mind'. Since then, the specificity and complexity of these responses have become increasingly clear. Sophisticated technologies have demonstrated effects within the brain that mimic and overlap with the effects of venum treatments for conditions such as chronic pain [3], Parkinson's disease and depression [4]. One of the problems for complementary and alternative medicine (CAM) as well as other complex psychosocial interventions is in distinguishing venum from placebo interventions, particularly when we are unclear about the exact mechanisms involved in treatment.

A recent review [4, 5] has challenged the notion that placebo is inert or that it should be considered distinguishable from its context, method of delivery, or the process of care-giving. Instead, it has been proposed that placebo be redefined as 'the simulation of an active therapy within a psychological context' [4, p. 507], reflecting the capacity of the human body to produce therapeutic and side-effects identical to those of active treatment in response to a range of environmental factors that influence the patient's expectations, desires, and emotions. In clinical trials that involve treatment of chronic pain illnesses, it appears that the major therapeutic effects of any intervention are non-specific and contextual rather than specific [6, 7]. This is not only true for CAM but equally applicable to other medical interventions such as the use of antidepressant medication [8], chronic pain [3], and Parkinson's disease [9]. The importance of 'active treatment' within CAM may considerably affect the outcomes and contexts in which they are administered, the expertise and authority with which they are delivered, the processes of investigation, diagnosis and treatment, and the rituals that accompany these, as well as the nature of the intervention and its method of delivery, all of which have been shown to influence outcomes [9, 10] and have the potential to exert strong influence on the clinical outcome of CAM interventions. A review of the evidence from clinical trials [1] identified a maximum effective size for placebo as 0.59 (95% CI classified as large) [11]. This would appear to demonstrate that significant therapeutic benefit is potentially available from placebo alone.

While placebo-controlled randomised controlled trials (RCT) are firmly established as the gold standard for testing the clinical effects of medical interventions, it is not always possible to employ effective placebo in situations that do not involve pharmaceutical agents. Michael Fischlin in his recent Harvard lecture draws this to our attention and suggests that we need to consider a broad range of evidence when evaluating data related to specific therapeutic effects [2]. Walsh et al. address similar issues in their view of appropriate evidence synthesis [13], and Gabbay and Le May clearly demonstrate that clinical decisions are frequently not dependent on the classical pyramid of evidence-based hierarchy [14]. We may not be completely dependent on the placebo-controlled trial for evidence of clinical effects but nevertheless, it will continue to be an important part of evidence-based medicine and the evaluation of specific clinical effects for a variety of interventions, particularly those involving conventional medications. The RCT was originally designed to evaluate the effectiveness of drugs for which identical placebo substances can be delivered using 'double-blind' procedures where neither patient, nor practitioner, nor researcher knows which treatment is 'real'. In this paper, we consider the problems arising from this approach, based on our practical experience as a sophisticated group of CAM researchers who have been involved in evaluating a number of different complementary therapies. We will consider the implications of these observations within the context and meaning of placebos for CAM and its rigorous scientific investigation within the complex debate that currently surrounds evidence-based medicine. We do not think that placebo-controlled trials are the only basis for clinical decision making but they are an important element of clinical evidence.

At each of the following sections is written by an individual who has both clinical and research experience in that specific field. The main research question we address is whether it is currently possible to design reliable, effective, and realistic placebos in these therapies. Do we understand enough about the interventions to know when we are using a placebo?

Providing a Placebo for Acupuncture Research

Researching an intervention which is clearly invasive can be very challenging. The central issue for acupuncture research is whether we can investigate a non-pharmacological invasive intervention in the same way that we can investigate a drug? Acupuncture is best described as the insertion of very fine needles into the body at varying depths according to the underlying structures. These needles are routinely manipulated to produce a sensation defined as 'Deqi' or needling sensation, before they are deemed to have their full effect [15]. There is evidence suggesting that the neurological networks responding to acupuncture are stimulated both centrally and peripherally carrying the impulses from the peripheral sensory input into the spinal column and up to the higher centres [16]. This raises a number of problems with 'placebo' acupuncture if we adhere to the criteria for a rigorous randomised, controlled clinical trial methodology.

In order for acupuncture to have the full effect, the patient must actually feel it, meaning that a directly comparable
placebo must also be 'felt'. Lundeberg et al. [17] have suggested that the general parameters for treatment for painful conditions with western acupuncture are well-established; the needles should be inserted to a specific depth, treated for a defined period of time, and used on a reasonable number of occasions [17] in the treatment of any clinical condition. If these parameters vary substantially, the patient will be aware.

While some may disagree with Lundeberg, the majority of RCTs using western acupuncture for pain do follow these very general guidelines.

A single application of acupuncture is rarely enough to produce the cumulative neurochemical and clinical changes which are thought to underlie the effect of this intervention. If it is thought by some [18] to be an essential neurological component of acupuncture, but if it can be elicited with a placebo, then, while this makes the placebo valid in the eyes of the patient and the researcher, it potentially confounds the outcome of any trial. Placebo needles, resembling stage daggers collapsing into their handles, have been used with some success [19, 20]. These do not penetrate the skin, although the sensation felt by the patient, who cannot see the tip, is usually convincing. Use of these needles is not straightforward and involves considerable skill on the part of the researcher [21]. While this has the potential of being able to blind the patient to the type of acupuncture received, the operator cannot be blinded as the two needle techniques are quite different [21]. A newer version of these needles is now available [22], where it is claimed that it is possible to blind the acupuncturist by having the needle, already within the plastic insertion tube, either inserted into some soft material at the skin or directly into the skin. There has been no substantial research completed using these new needles.

The main problem with all of these sham needles is that the intervention is of a completely different kind such as a sham acupuncture laser or TENS stimulation. This would provide a central intervention for real acupuncture that would not be a direct placebo and its validity would depend on the patient rating the two interventions equally.

Most conditions which present for treatment with acupuncture are self-reinforcing making it even more difficult to be sure that the specific effects of the therapy are responsible for all or any of the recorded changes. With a complex intervention, the attributable effect becomes smaller the more rigorous the study design.

It is not really possible to indicate how much of the total effect may be represented by each of the components suggested in table 1 but it is probable that spontaneous changes vary from condition to condition, while the associated or context effects may vary depending on the type of consultation taking place. It is also probable that the practitioner is the most important variable [9]. Clearly where there is both an element of ritual and an extensive clinical interview, the placebo effect of the intervention will be reinforced substantially [23] and may be both practitioner and dose dependent [10].

Some very valuable work has been done within acupuncture to indicate that there is more than a placebo effect [5]. Using positron emission tomography (PET) scans the effect of a sham needle involving superficial sensory stimulus only has been eliminated, together with the additional effect of the patient's belief and expectation, leaving a visible effect in another part of the brain entirely.

This raises an important ethical question. Some acupuncture trials in Germany with substantial patient numbers and careful methodologies have failed to demonstrate a significant difference between the placebo and verum acupuncture interventions [24-27]. Where the specific effect is so small, the importance of this technique is either vital or really irrelevant. The question is which?

It is understandable that we require a clear answer as to what the exact physiological effects of acupuncture may be and how they can be best reproduced. It is equally clear that the clinicians might prefer to use the research process to refine the context in which a therapeutic intervention is designed and thus improve its effect. In view of the fact that acupuncture appears to be more effective than conventional care for many conditions, even if it is a placebo [28], the next question is whether it would be unethical to withhold acupuncture in clinic (VH).

Is Homeopathy a Placebo?

One of the challenges that affects research into homeopathy is the uncertainty surrounding the plausibility of the homeopathic remedy. This has led to research that has consistently attempted to find specific effects of homeopathy from the remedy alone, treating the remedy as if it was a biomedical

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drug with specific physiological effects. Such a focus has lead to conflicting evidence about efficacy [20-24] suggesting that the clinical effects of homeopathy are placebo effects which are a result of the therapeutic encounter that is experienced as part of the consultation [25, 26-29].

The challenge of researching homeopathy is compounded by the poor quality of many homeopathic trials compared to clinical trials in conventional medicine [40]. Additionally, the RCT has frequently not investigated homeopathy as it is practiced in a "real world" setting. For instance the blinding of homeopathy participating in a clinical trial interface with their normal practice routine of an individualized patient response to a far greater extent than with a conventional medical prescription [41]. Furthermore, the use of isopathy is not a routine part of classical homeopathy [42, 43].

The value of examining the specific effects of a therapy (the remedy) as separate to the non-specific effects (the effects from the practitioner-patient relationship etc.) of a therapy has been questioned. For example, it has been proposed that homeopathy is that specific and non-specific effects may interact rather than just being additive effect of the homeopathic intervention [41]. This view is reiterated in Paterson and Dieppe's [44] observations on acupuncture research. These and other challenges can be addressed by thoughtful design in the application of RCT method investigating CAM, for example, the use of pragmatic approaches [45], and by combining RCTs with qualitative methods [46].

In order to fully understand a CAM intervention such as homeopathy, research must address its separate components, whilst allowing the system to remain intact because of synergy between the different components [46]. The process and context are fundamental to effective treatment and positive outcomes for any therapy, not just homeopathy [46]. The process and context of a therapy refer to components such as the relationship between the patient and the practitioner, expectations, and how an intervention is delivered. The therapists' contribution to these components can only be understood by exploring the consultation in depth from the practitioners' perspective.

My research into the nature of homeopathy has focused on understanding homeopathy and how they consult so that we may better understand the nature and models employed by them during a homeopath consultation. This has enabled me to recognize the power of the therapeutic interaction in the homeopathic consultation which includes the use of a remedy. I have explored homeopathic practitioners' experiences and perspectives of the consultation and have developed a theoretical model of the process of the homeopathic consultation from a perspective which demonstrates that the practitioner-patient relationship is encoded to all the processes in the homeopathic consultation. The process of identifying, choosing, and giving the homeopathic remedy appears to be specific to homeopathy as it has a central role in the homeopathic consultation and may therefore play an active part in promoting therapeutic benefit. My findings corroborate a previous theoretical explanation by Weatherley-Jones [41], in that the homeopathic remedy cannot be treated independently to the effect of the consultation. I have therefore concluded that the remedy is meaningless to separate the remedy from the consultation. This is consistent with the theoretical model of entanglement in homeopathy between the patient, the practitioner, and the remedy [47, 48].

In my recent work, I have been investigating the terms "placebo" and "non-specific effects" as a means to explain the nature of the catalyst for the specific mechanism that is activated within homeopathy as a whole system. The term "context effects" is an alternative explanation that has been proposed as an alternative to the idea that a placebo is just a placebo, implying that there is a specific effect of treatment interventions which is inherent with any homeopathic consultation. In recent years, it appears the homeopathic remedy is an indivisible and specific part of the homeopathic consultation.

Therefore, an alternative explanation is needed. A framework that sits comfortably within the findings of my research in Moerman and Jonas's [50] concept of the "meaning response" which relates to the response that people experience as a result of the meanings that they attach to their interventions or treatments. Similarly, motivational concordance points to the fact that a particular treatment is in accord with the patient's own preferences and motivations, then the patient will be more likely to engage in that treatment, and it is the degree of engagement in the treatment that may lead to symptom reduction [51]. An important part of the homeopathic consultation is the narrative aspect which elucidates connections and meanings [52], and these can be symbolically represented by the homeopathic remedy [53, 54]. This framework takes into account the different meanings of the terms "placebo effect" and "context effects" and allows an understanding of these terms within a cultural context that allows for the complexity of meanings, rituals, and symbols that are attached to the objects and activities that contribute to the homeopathic consultation. (CE)

**Kinesiology**

In my role as a practitioner-researcher, I was interested to develop a sham kinesiology intervention to attempt to discover whether there was indeed a specific treatment effect over and above the non-specific effects, but as the mechanisms of kinesiology are as yet unclear, providing an inert treatment as a control was challenging. Nell et al. [55] suggest that a plausibly ineffective placebo treatment was required to control for the potentially therapeutic effects of
touch in manual therapies. Therefore, the sham treatment needed to look as much like the real treatment as possible, be credible to patients, but be devoid of anything considered therapeutic in kinesiology theory. Kinesiology appears to be a complex whole-system intervention utilizing touch, talking, techniques, and lifestyle change and it is not clear what the active ingredients are or how they relate to each other. Furthermore, these factors are not necessarily additive but may be synergistic. It was clearly not possible to perform any treatment without touch but it was possible to limit the conversations of the placebo group to theoretically benign subjects controlling for the effect of touch in both groups. Despite these challenges, I have recently developed an apparently credible sham treatment designed to be minimally effective for use in a single-blind RCT [54]. This has been a complex procedure but it has resulted in the development of the standardized sham (placebo) Kinesiology process that will begin to allow us to separate the specific and non-specific therapeutic elements of this intervention. At this point, it is impossible to know if Kinesiology has any specific active components or what constitutes its specific or non-specific intervention within a Kinesiology context. A true placebo for Kinesiology still seems a long way away! (SI)

Healing

Physical healing, whilst probably one of the oldest medical treatments, is a comparatively neglected area for research, yet there is a growing recognition of the importance of physical well-being in patient care [57, 58]. Anecdotal evidence for spiritual healing suggests that it is a multi-dimensional therapy that operates in several domains simultaneously [59]. Healing (those receiving healing) can experience profound relaxation which can alleviate stress, anxiety, and the perceptions of pain while experiencing feelings of well-being and empowerment [60-63]. While some consumers appear content with anecdotal evidence about the clinical effects of healing, there is a pressing need for solid evidence of effectiveness and safety, if healing is to be widely used in support of orthodox medical interventions.

Discussions around spirituality and health care can combine a myriad of concepts including 'miracle', cure, ritual, prayer, meditation, and healing, while spiritual healing itself has been linked erroneously to the occult and religious practices rather than an energy-based CAM therapy. Spiritual healing is a generic term which includes Reiki and House and does not diagnose, prescribe, seek, or claim a specific therapeutic outcome; it does not seek to cure in a medical sense but claims to address the symptomatic needs of a patient and involves a holistic approach to mind, body, and spirit. There are two distinct forms of spiritual healing, contact and distance healing given in the presence of the patient and distance healing where the patient is absent. Distance healing can be distinguished from prayer which seeks the intervention of a higher being to facilitate a specified result. In studies of both distant and contact healing, it is possible that patients who resent into a clinical study may have expectations linked to their enrollment which may not replicate real-world therapeutic interaction and thus, the content in which the therapy is given (or not given) may be crucial to the outcome [13].

The two forms of spiritual healing present different challenges for the researcher. Walfach et al. [64] have demonstrated that the expectation of actually receiving a therapy may play a significant role in the outcome of distant healing. In contact healing there are likely to be additional non-specific effects due to the various healer-patient interactions within the therapy session. It is also unclear if healer and placebo intervention influence the healing outcome and how these factors might interact [65] and whether models such as entanglement and wave quantum theory might explain healing [66], the exact mechanisms are unclear. Therefore, sham or placebo healing could be working through exactly the same mechanisms as real healing and may therefore not be true placebos. Furthermore, systematic and critical reviews of healing studies have found the methodology of many of the published RCTs inadequate [67-71]. These criticisms include issues of blinding, inadequate power, and the poor reliability of the outcome measures employed.

Healing organisations claim everyone has the potential to heal, thus actors [68, 72-74] and trained healers [75, 76] may be delivering healing unknowingly to themselves or others. In the light of such confusion it would be inappropriate to use placebo healers in RCTs of either contact or distant healing. Thus, studies of spiritual healing are challenged to generate knowledge about this holistic therapy when research methods such as RCTs are designed to isolate and examine specific elements of any intervention. It would seem that a mixed-method approach designed to address whole complex interventions is necessary allowing initially qualitative methodologies to inform further research [78, 79]. It may also be valuable to consider approaches that involve waiting list controls [59, 80, 81] or pragmatic studies that address the overall effectiveness of healing [82].

As a consequence, I have chosen, in my role as a practitioner-researcher, to employ qualitative methodology to understand breast cancer patients' experience of contact spiritual healing delivered by a group of healers. Using unitary appreciative inquiry [83, 84] allowed the patients on the study to be involved in the conceptualisation of the results at each stage of the study, avoiding researcher bias and informing further research. This will allow me to model the process of healing from the patient's perspective and through this better understand the individual mechanism involved. It is only with the level of rigour, that we will be able to have any real chance of developing a credible and viable placebo within this field. (FB)
Chinese Herbal Medicine

Over the past 40 years, at least 17000 RCTs have been conducted in China investigating the effectiveness of Traditional Chinese Medicine (TCM) [83, 86], with the majority of these trials related to Chinese herbal medicine (CHM) [8]. However, whilst there is a vast and growing corpus of CHM research, its value as an evidence base has been compromised by a lack of methodological rigour and transparency [90]. Inadequate randomisation, small sample size, and lack of blinding in particular have left the interpretation of this research vulnerable to the disturbing effects of selection, reporting, and assessor biases.

The balance between rigorous and relevance is particularly difficult to achieve in CHM. Rigour can and has been introduced by proper randomisation and enhanced by placebo controls that have been evaluated for their credibility in a number of studies [87, 88]. However, CHM as it is most commonly practiced involves a decoction (boiling up) of a complex formulation of herbs that changes according to individual presentation and again will be adjusted several times during the course of treatment. This is difficult to match with an equivalent and convincing placebo and so the tendency has been to either standardise the decoction or omit the decoction altogether and rely on unprepackaged herbal powders or pills to deliver both venum and placebo treatments. Despite the pragmatic appeal of these designs, neither a standardised decoction nor manipulation are generally considered as examples of optimum CHM practice. Relevance is diminished to suit the requirements of rigour.

However, as part of a feasibility study exploring the role of CHM in the treatment of endometriosis, we have designed a novel methodology that manages to combine relevance with rigour. Using simple extraction technology imported from Korea it has been possible to dispense individualised decoctions for each trial participant in the active arm of the trial that can be matched with a placebo decoction made from commonly used vegetables and culinary herbs available in the UK. The decoction is prescribed for the patient to take twice a day for seven days. It is then returned to a distillation pharmacy where it is randomised to active or placebo, cooked, and then sent to the trial participant. Both venum and placebo are strong tasting and dispensed in identical sealed packets. This allows for a double-blind, placebo-controlled RCT.

The trial has now completed and blinding was successful with neither recipient nor practitioner able to reliably predict group allocation. Patients in both groups showed significant improvement and we were able to identify a clear and powerful response to placebo CHM as well as real CHM treatment. An obvious problem with this approach is the possibility that the common foods that we used could have had a therapeutic effect. Even so, it seems reasonable to expect a focused herbal intervention to be able to demonstrate a better therapeutic effect than what is effectively a glorified vegetable soup.

The next stage is to develop a placebo using food flavonoids which have no active compounds and can be more readily regarded as inert. This is now entirely possible and should enable a more effective placebo-controlled comparison.

There is a danger that in comparing active and placebo harms we will focus on the specific effects of CHM and exclude the contextual effects of CHM intervention. CHM is a whole-system medical system [9] that has developed extremely effective ways of enhancing the contextual effects of treatment including a sophisticated enhancement of the therapeutic relationship via an in-depth diagnostic process that is highly attentive, intuitive, and caring. Pulse diagnosis, for example, involves the practitioner maintaining a steady and relaxed contact with the patient for several minutes, which is both diagnostic and probably therapeutic. CHM diagnosis frequently uses metaphors and idioms such as ‘hot’, ‘cold’, ‘flaring of Fire’ that manage to be both slightly mysterious and exotic but is also precise and resonant to the patient’s experience of their illness. In many ways, the contextual effects of CHM are uncharted territory, although there are obvious parallels with work done on the importance of the consultation in acupuncture [9]. However, it is extremely likely that these effects exist and that they constitute an important component of the therapeutic effect of the treatment. The danger is that if we are looking to test the active herbs against the placebo, we may be excluding other active effects of the whole-system of CHM intervention. While intellectually interesting, this is not an accurate pragmatic assessment of the clinical effects of CHM.

One possible way around this obstacle would be to have a waiting-list control as a third arm. This would enable a comparison of active and placebo groups leading to an estimation of the specific and contextual effects, respectively, of treatment. However, waiting-list controls may have a high dropout rate and being in the waiting-list group is not a neutral or ‘inert’ act. Restitution, anticipation, and other responses to being in this group could easily introduce their own confounding effect.

It seems that we have to accept that any research design has the capacity to introduce its own bias. All measures of specific, contextual, or combined effects of treatment are going to be compromised by the complexity of the human experience who react in unpredictable and idiosyncratic ways to their health care. However, with these limitations in mind we should still proceed cautiously with placebo-controlled trials. They will allow an estimate of both the overall and the specific and contextual effects of treatment which will help to establish the extent in which CHM may be most able to contribute to health care in the West, to explore the healing effects of the consultation process, and at the same time to identify and refine our understanding of key components of treatment relating to, for example, dosage, herb selection, and method of administration. As long as we are mindful that ‘placebo’ is in-built into the whole-system of CHM and indeed all medical interven-
Conclusions

We are aware that placebo-controlled randomized trials are a single and limited scientific tool. However, clearly placed this in context when viewing the RCT as one of the many mechanisms of obtaining valuable clinical evidence [12]. In this paper, we are simply focusing on the design of appropriate placebo controls for particular CAM interventions and the scientific issues that arise, rather than primarily addressing the whole-contextual debate about best methods available for obtaining clinically relevant evidence for the treatment of many chronic conditions. Our research group has been working together for over 16 years now and we have consistently addressed the issues of credible true placebo controls in the context of the clinical trials we have designed for specific CAM therapies. Some of our mechanistic investigations have indicated that real placebo may be possible in such fields as acupuncture and homeopathy [5, 56] but we are also too aware that consequently placebo may simply be neither credible nor indeed possible at the moment for some interventions such as spiritual healing. Each of the therapies considered in this article are at slightly different stages in their research development. Consequently, each CAM intervention requires a slightly different strategy in relation to addressing the nature of placebo and the specific and non-specific components of any particular intervention. We hope that our discussions around each intervention not only show our ability to develop and innovate, but also address the problems that investigating whole medical systems such as TCM and homeopathy must address within the context of placebo-controlled trials [8, 9, 90].

We do wish to create a rigorous but thoughtful scientific environment through which CAM can be effectively used and evaluated. We believe that first we need to pay particular attention to the underlying mechanisms that may be involved in each therapy and therefore, the identification of a true placebo if that is possible, and how this should be developed in the context of a clinical trial. This will be through a combination of qualitative modeling and the investigation of the basic biochemical, neurochemical and physiological pathways involved in each therapy. We will then need to carefully evaluate the effects of various experimental placebo within RCTs specifically designed to address the feasibility of delivering the placebo intervention as well as its credibility. Finally, we should begin to have placebo that will be credible, visible, and can be realistically delivered within the context of a randomized study.

We also underscore the methodological debates and limits of the placebo-controlled RCT and would argue that those who wish to absolutely reject the placebo-controlled RCT are equally as foolish as those who see it as the only rigorous methodology that can reliably evaluate clinical effects. The placebo-controlled RCT has its part to play within the context of clinical evidence but it appears that its dominant role is being challenged effectively by health service researchers and the use of sophisticated pragmatic trial methodology [51]. We are only too aware that whole-systems research [89, 91] may demand substantial changes in our strategic approaches and furthermore that we may need to look at evidence in a non-hierarchical manner [13]. As with acupuncture [5], it is very likely that our assumptions about the specificity of needling within the context of acupuncture as a whole-system is incorrect. It could be that there are therapy-specific effects which the clinical trial may deem non-specific by virtue of its design and focus on acupuncture point specificity. What is clear is that this is a complex area where both context and the often un-substantiated therapeutic assumptions about specificity within different CAMs need to be examined with care and rigour.

If we are to rationally develop such placebos for the purposes of rigorous RCTs, then a coherent research strategy is required which takes into account the context of the intervention, its impact as a whole system, and its potential mechanisms. Acupuncture is a good example, and while it may have been very reasonable to think that acupuncture was simply about needling a particular point on the body 30 years ago, our current understanding of the process of acupuncture and its mechanisms makes this now appear both ridiculous and unscientific. This is clearly an area where both context and often unsubstantiated 'traditional' assumptions about therapeutic specificity within different CAMs need to be examined. It is apparent from our collective experience that simply 'inventing a placebo' for a particular trial might sound attractive, but methodologically must represent great intellectual poverty and fundamental misunderstandings in scientific thinking. This process requires careful and thoughtful development if we are to continue to use placebo-controlled trials to provide us with relevant, appropriate and valuable clinical evidence for CAM interventions.

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