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Original article

Complementary alternative medicine and conventional medicine should use identical rules to complete clinical trials

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Abstract

Considerable time and debates may be dispensable if it is accepted and respected that the underlying concepts, beliefs, and assumptions in complementary alternative medicine (CAM) and conventional medicine (CM) are different whereas the methods to demonstrate efficacy and effectiveness of these concepts may be identical. We discuss in this paper that the formulation of precise questions may led to a consensus on the methods to be used in clinical trials of CAM and CM. To demonstrate that identical methods may be applied in CAM and CM we suggest using a sequence of ten steps. Six of these 10 steps are identical in CAM and CM while four steps are only similar. It is important to recognize that two of these four steps are applied in a different sequence in CAM and CM. The formulation of precise questions and the application of adequate methods may provide the basis to compare, evaluate and justify both approaches, CAM and CM.

Keywords: Explanatory trial; Pragmatic trial; Clinical trial; Methods

There are many discussions and proposals for the conduct of clinical trials in complementary alternative medicine (CAM), but only few systematic approaches about this topic have been published [1–3]. Important activities in this field are the National Center for Complementary and Alternative Medicine (NAAAM) which is the lead research and educational institution for CAM and a database provided by the office of cancer and complementary alternative medicine of the NCI [4]. Despite of these activities there is only sparse evidence as compared to the huge amount of personal experience provided by many patients and clinicians who are convinced about the effectiveness of CAM in daily clinical practice.

This lack between formal evidence and convincing personal experience should be addressed by scientists. The precise definition of the goals of interventions is a first step. Only if the goals are clearly defined it will be possible to confirm the goal attainment. The "Framework for Design and Evaluation of Complex Interventions to Improve Health" which was published by the UK Medical Research Council [5] can be effectively implemented only if the problem which should be solved has been properly addressed.

To solve these problems it is increasingly accepted that there are two types of clinical trials which describe the continuum [6] of a spectrum of trial designs [7–12] with the endpoints of the explanatory trial and the pragmatic trial. While explanatory trials try to identify a potential cause of an observed effect by testing an intervention under optimal and ideal conditions (efficiency trial) and by excluding any external factors that may influence the results, the pragmatic trials describe just the opposite, i.e. a particular effect under realistic day-to-day conditions (effectiveness trial). Accordingly, the latter include all confounders that cannot be avoided under real world conditions. It should be emphasized that the definitions of explanatory and pragmatic trials vary among authors. Ernst and Canter [13] recently stated

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Table 1
The ten recommended steps in explanatory and pragmatic trials.

Step	Explanatory trial	Pragmatic trial
1	Define the type of research (explanatory or pragmatic trial) that should be completed	Define the type of research (explanatory or pragmatic trial) that should be completed
2	Phrase the (four parts of the) precise study question according to the principles of evidence-based medicine	Phrase the (four parts of the) precise study question according to the principles of evidence-based medicine
3	Select the most appropriate study design within the groups of explanatory and pragmatic trials	Select the most appropriate study design within the groups of explanatory and pragmatic trials
4	Confirm the selected study design can be used in a confirmatory study	Confirm the selected study design can be used in a confirmatory study
5	Define inclusion/exclusion criteria and the treatment options	Define the patient's risk groups and the treatment options
6	Ask eligible patients to sign the informed consent (IC) for randomization, blinding, treatment and collection of data	Allocate all patients according to "doctors and patients preferences to treatment options or to "other treatment"
7	Allocate the eligible patients with signed IC randomly to the treatment options	Ask all patients to sign the informed consent for evaluation and publication of the data
8	Guarantee a follow up that is long enough to observe a sufficient number of endpoints	Guarantee a follow up that is long enough to observe a sufficient number of endpoints
9	Analyze the results according to the ITT principle	Analyze the results according to an ITT-like principle
10	Confirm statistical significance of the clinically relevant results	Confirm statistical significance of the clinically relevant results

ITT: intention-to-treat analysis. The difference in the sequence of corresponding steps 5–7 and in step 9 explanatory and pragmatic trials is highlighted by different colors.

appropriately that some of these definitions are indeed too weak to generate any reliable results.

We discuss in this paper proposals for study designs which may be identical in treatment studies of CAM and CM but depend on the exact definition of the study question in both CAM and CM.

The proposal suggested in this paper is based on a Gedanken experiment [14,15] considering methodological details that may be used in clinical trials when either the potential causes of a therapeutic intervention or the outcome under real world conditions are to be investigated. We denominate the first type an explanatory trial and the second a pragmatic trial. In the first type, the explanatory trial, comprising five steps of knowledge gain can be identified according to the UK Medical Research Council [5]. In the second type, the pragmatic trial, the main goal is the documentation of an expected effect under real world conditions. Ideally, the internal validity of the effects has been demonstrated first in an explanatory trial under ideal conditions before the external validity is confirmed under real world conditions. It should be mentioned here that not in all cases this ideal constellation of an explanatory and a pragmatic trial will be possible. The idea has been discussed in our group for several years [16,17] a considerable budget is now provided by the US government for comparative effectiveness research [18].

Our proposal

Our proposal is based on 10 steps for explanatory and pragmatic trials. Six of the ten steps (step 1–step 4, step 8 and step 10) are identical in explanatory and pragmatic trials. The remaining four steps (step 5–step 7 and step 9) are similar. It is however worth mentioning, that the sequence of step 5–step 7 is different in explanatory and in pragmatic trials due to an inductive approach in explanatory trials and a deductive approach in pragmatic trials.

Step 1: The first question should be related to the type of research project which is planned. If the potential cause of an observed effect will be investigated, an explanatory trial, i.e. an efficacy trial is appropriate. If the effect of a treatment under day-to-day conditions should be investigated, a pragmatic trial, i.e. an effectiveness trial is the optimal approach.
Step 2: The second but not less important step in any experiment is the formulation of the correct study question. The strategy suggested by the Evidence-Based Medicine Group [19] and modified later [20], is helpful in posing the appropriate question. This strategy recommends the definition of four parts of this question. Firstly, the precise characteristics of patients who should be included in the trial and the disease of these patients have to be described. Secondly, the objective of treatment has to be given in detail. We recommend also a description of the dimension according to which the attainment of the objective will be assessed. Thirdly, the experimental treatment and fourthly, the control treatment have to be described. If there is no other treatment option that could be compared with the experimental treatment, an untreated group may serve as control. In this case it should be considered that the observed effect of the experimental treatment might be not stronger than any placebo effect.