Robert Bosch Stiftung

International Workshop on Study Methods in Complementary Medicine

Minutes of the Meeting

20 and 21 April 2006 Stuttgart, Germany

Content

1. Opening

Speaker:
Dr. Ingrid Wünning, Robert Bosch Stiftung

Since its foundation in 1964 the Robert Bosch Stiftung has carried on the charitable endeavors of its founder Robert Bosch. One of his lasting monuments has been his commitment to homeopathy. He was one of the major patrons of homeopathy in Germany during the 20th century and amongst other things tried to initiate hospitals, focussing on homeopathy. From their establishment, the hospitals were asked to explore the efficacy of homeopathy with the best available study methods. Although for a number of reasons homeopathy disappeared from the Robert Bosch Hospital in Stuttgart in the early 1970s, the Stiftung is still promoting research into complementary alternative medicine (CAM) in general with particular emphasis on homeopathy. One crucial problem in this field is the evaluation of the efficacy of complementary medicine. The Robert Bosch Stiftung invited experts to discuss this matter on the 20th and 21st of April 2006 in Stuttgart.

In her introduction, Ingrid Wünning from the Robert Bosch Stiftung explained the background of the initiative. Despite the fact there were already several different international initiatives, the Stiftung decided to carry out another workshop. The strategy for the workshop was to define the current state of debate with a view to answering questions like: Are there study designs particularly suitable for complementary medicine? Are there any trial methods which could be accepted both by conventional and complementary medicine? According to Ingrid Wünning the situation in relation to the clinical evaluation of therapy in CAM is far from clear and it is essential to check the current status of the subject. During the workshop this assumption proved correct. The question of who should be involved in research on CAM also played an important role in the discussions.

The many issues addressed in the workshop demanded a broad range of different professional skills to be represented at the meeting. The group of 29 participants included complementary physicians, conventional physicians, foundation managers, biochemists, psychologists, statisticians and experts of computer science and even historians of medicine.

2. Introductory Remarks: Study Design and Methods: The State of Present Knowledge

Speakers:
Dr. Klaus Linde, Technical University Munich, Center for Complementary Medicine Research
Dr. Jos Kleijnen, Kleijnen Systematic Reviews Ltd.

The contributions to the first sessions were primarily devoted to setting the stage and to reviewing knowledge on the diverse aspects of study design and drug testing. **Klaus Linde** and **Jos Kleijnen** presented introductory remarks on the subject which were followed by a panel discussion.

Linde came back to Ingrid Wünning's question "Why again a conference on study design?". Linde demonstrated that "30 years of countless conferences and workshops on study methods" could not diminish the ambiguities and uncertainties of the trials in complementary medicine. He raised particular doubts about the impact of randomized clinical trials (RCT) for study design in CAM. Although the clinical research focus had been on RCT the results have been disappointing and ambiguous. For example, more than 150 RCTs in the field of homeopathy could not deliver clear results and therewith could not stop the controversy about the efficacy of homeopathic remedies, although homeopathy appears to be safe and effective in medical practice. The same is true in herbal medicine (e.g. St. John's Wort) and acupuncture in the treatment of chronic pain – examples which Linde cited to underline his argument. The reasons for many uncertainties are not only the conflicting study outcomes but also the fact, that "not a single CAM therapy (…) has been really proven to be more effective than placebo". Although some general problems such as the huge area of research and the limited financial and intellectual resources were mentioned, in Linde's view the narrow approach of researchers to the evaluation of clinical outcome is much more problematic. Clinical research in CAM needs to be diversified: All types of RCTs need to be considered, more outcome studies and single case studies need to be carried out and more work on mechanisms of efficacy should be funded. Above all the mere division of the efficacy of a treatment into "beneficial" and "not beneficial" in terms of specificity is far too restrictive, because it leads to a neglect of the substantial "non-specific effects" of diverse CAM treatment procedures and medications. Because of these "non-specific effects", RCTs with placebos, which have also "non-specific effects", make no sense and are impossible to interpret. But even if there are only "non-specific effects", CAM might help the patient. Instead of searching for "specific effects" to make CAM "scientific", one should analyze the "non-specific effects". It is unimportant, whether a therapy is "scientific" or not, but it should help the patient and - if it is safe and beneficial - it should be an available treatment.

Whereas Klaus Linde presented a critical report of practical problems with the performance of RCTs and the current problems for clinical trials in the evaluation of

CAM, **Jos Kleijnen** insisted on the importance of standardized clinical trials for studies in both conventional and in complementary medicine. His paper was based on the principles of evidence-based medicine (EBM), which were applied to the problem of CAM studies. The latter definitely need standardized research methods and subsequent systematic reviews. This allows for "pebbles" of knowledge to be changed into "gems". The main issue for Kleijnen is the adequate planning and performance of studies. There should be appropriate questions, adequate objectives, a careful study design and the best available evidence. Kleijnen admits that specific research methods are needed by CAM but they should be comparable with those of conventional medicine. In summary, the consideration of the principles of EBM are the most important factors in determining the quality of CAM research.

3. Panel Discussion: Studies in Complementary Medicine: Choice Methods – the Choice of the Method

Speakers:
Professor Dr. Walter E. Aulitzky, Robert Bosch Krankenhaus
Dr. Roman Huber, University Hospital Freiburg
Dr. Andreas Michalsen, Kliniken Essen-Mitte, Department of Internal and Integrative Medicine, University Duisburg-Essen
Moderation: Lilo Berg, Berliner Zeitung

The tension between the preceding presentations was felt in the following **panel discussion**. It was chaired by the journalist **Lilo Berg**. Participants were three clinicians: **Walter Aulitzky**, **Roman Huber**, **Andreas Michalsen**. The comments of all three participants focussed mainly on three topics, which proved to be important for the further course of the conference and which were taken up several times:

The problems in connection with CAM trials: The discussion group agreed with Klaus Linde about the complex conditions of study design in CAM and doubts about the quality and interpretation of CAM studies were taken into account. In general, the performance and rigor of studies clearly need to be improved because many specific issues in many CAM therapies are still unclear.

One of the crucial basic problems of study design is the type of patients, who are willing to participate in studies, namely those with chronic diseases. There are often not enough patients for randomized trials. The compliance of patients in studies also causes problems. Many patients are happy to participate in randomized studies to test drugs which are not on the market, but there are not many, who agree to be involved in trials on drugs which are already available but need further testing. The CAM patient often wants to receive a specific therapy particularly if it is already well known and widely available.

What about the future? Are there any options to improve the performance of clinical trials in CAM? The participants of the discussions raised questions about the quality and focus of studies but agreed that more trials are needed. Also, the range of different study designs should be exploited more effectively: Especially important is the increase of observational trials for chronic diseases, although such studies are currently not well regarded. Another aim is to raise quality standards. In order to increase validity large studies are desirable, but these studies have the same problem as life-style studies: They are hard to organize because a lot of data from different sources needs to be collected and analyzed. Furthermore, they are very expensive. The leading question when doing these studies should be: Which patients will benefit?

Which therapeutic agents or methods should be tested? To make CAM trials more feasible the cheap remedies should be evaluated initially as well as those which some initial evidence of clinical efficacy. Therapies with well understood mechanisms of action should belong to a target group of substances and approaches worth investigating in more depth (e.g. herbal medicine and acupuncture). But there is not enough funding for such studies and the proposal was made to try to enable much more public funding. Current financing of studies lies mainly in the hands of the pharmaceutical industry which has specific self interest when spending money on research.

The role of the patient. The discussion was very much shaped by ideas about the role of the patient in the setting of clinical CAM studies. One of the crucial questions about the effect of CAM remedies is whether the patient benefits or not. Benefit is not always linked with a *restitutio ad integrum*, a complete cure. The patient needs the physician also as a supporter, helping hand and advisor. CAM profits from the lack of time of conventional physicians and ”disturbed” communication with the patient as a consequence of limited time. The question of whether the studies solely focused on the “remedy” are “scientific” is not the only decisive point and is of minor importance compared with the overall benefit to the patient of the whole treatment process. The role of media reports and the way they influence the views of patients using alternative medicine is unclear. It often seems to be the case that patients believe in specific therapeutic methods and therefore are immune to negative media reports about CAM. Some patients adhere to CAM with great intensity because of their specific diseases and disease condition. Patients with cancer and chronic diseases are often keen to use alternative and complementary remedies as a last resort. Much more work has to be done to study the patient-physician relationship as a key factor to understanding CAM therapy and its clinical outcome.

The meaning of EBM. Although EBM is based on a consistent theory which works within its own system, there seems to be a major problem when applying it to CAM studies and therapy, and possibly also to conventional medicine. There is no academic or commercial infrastructure to perform clinical trials within CAM or to

review data collection on a larger scale. Furthermore, work in EBM is hampered by severe shortcomings in the protection of ideas and commercial patents thus complicating commercial investment in new treatments. Lack of public funding and academic credibility are also major issues.
Besides questions of introducing EBM standards into CAM practice, the meaning of EBM for CAM in general has to be analyzed. Who profits from the standardization produced by EBM? CAM therapy is a very individual therapy. The patients need, above all, a physician who can help; the individual setting and context of treatment is often not adequately considered in EBM.

The topics and questions raised by the panel discussion were in general taken up in the **general discussion**. But participants now mainly focussed on research studies which aimed to analyze the context from the patient's perspective. Context-related research was discussed in general and also in detail, when talking about the consequences of the approach on the performance and methodology of studies.

Context-related research in general: This debate demonstrated that CAM is only partially comparable with conventional medicine. The discussion was inspired by George Lewith, who presented the UK approach. Groups of specialists and interdisciplinary work would be needed to develop an understanding of the context of the CAM treatment and then design an appropriate research strategy. Interchange between physicians, anthropologists, philosophers and (medical) historians will form an essential part of this process. According to George Lewith, networking - above all on the national scale - would be very important in realizing some consensus about the ideal strategic approach. In the UK, "The Wellcome Trust" had set up Clinical Research Facilities within conventional medicine in University Hospitals that host CAM and conventional research on a competitive basis so that only the best projects are supported. Networks of such units could create co-operation and understanding between CAM and conventional researchers. This approach was welcomed directly or indirectly by nearly all participants of the discussion.

A broader approach should include different - also historical - concepts of health and disease as a basis to analyze effects of remedies. Different cultural concepts related to different specific strands of CAM, e.g. phytotherapy, should be mobilized to enlarge the spectrum of research questions. Many more studies should be carried out to investigate cultural aspects, expectations and context of CAM treatments.

Context-related research in detail: The discussion brought forward not only general arguments about this research strategy, but also suggestions for detailed improvements of clinical CAM studies.

New categories could be analyzed, e.g. empathy of consultations within alternative or complementary medical treatment, the *doctor-patient relationship* as well as the context of recruitment for CAM studies. The first consultation often provides con-

siderable insight into the therapeutic relationship. The patient's perspective as a consumer of CAM, his or her needs and their opinions and beliefs about CAM may have impact on the treatment outcome. It is equally important to look at the doctor's perspective and beliefs, which need much more attention in future trials.

Another topic was *gender-related questions*: The core factors: doctors, age and gender should be analyzed in greater detail. Currently there is no clear evidence for gender being an important covariate, but the analysis of some studies suggests that female physicians had less adverse therapeutic events than male physicians in acupuncture trials. Furthermore, according to some studies, women treated by female doctors made better therapeutic progress than those treated by male physicians.

We certainly need to reflect in much greater depth about the implications of trial *methodology* and the specificity of the *intervention*; for instance in acupuncture, where different approaches exist which need further analysis. For example, discussions are far too centered on the question of point specificy of the method, although this may not be the 'key' to the clinical effects obtained through acupuncture (Lewith). The results of the large German studies are not satisfactory in every aspect. What is needed is a diversity of different study methods. This means that non-specific effects as well as specific effects should be studied. Ethical issues are also important: For example, the ethics and process of sham methods are debatable as they could deprive the patient of beneficial therapeutic approaches (one example are the sham studies of bypass surgery in the 1960s). We can't really use effective shams without understanding the mechanism of the intervention which we are investigating as we may not be evaluating the 'effective' component(s) of the treatments. Another aspect was that a diversity of study methods also requires us to cultivate a diversity of skills. The CAM researcher needs to be able to apply a range of different skills. These skills also need much more focus and thought in future CAM studies.

The question is also whether the performance of *single case studies* should be championed. One already knows about successful therapeutic events in single cases, e.g. about homeopathic treatment supposedly healing leukemia. This example again reminds one of the importance of beneficence. But although there is some experience, further studies have to look much more closely at the history and progress of single cases. This would enable researchers to detect remissions caused by CAM treatment, e.g. in the case of carcinoma. Eventually it would be wise to make a best case selection – and these best cases may not be as rare as it seems at the first glance. To prove evidence, the correlation between the time of application and the time of effect of an alternative or a complementary treatment should be investigated more intensively. Furthermore one could use expertise of the Catholic Church, which has a medical commission to investigate miracles taking place at centers of pilgrimage such as Lourdes (Kraft).

Fundamental problems: Discussion concentrated on the lack of money and academic infrastructure, the need to publish the results, and the resulting difficulties for researchers in planning future CAM studies. These necessities demonstrate that the field of complementary medicine needs the same academic structures and rigor as conventional science.

The next two sessions of the meeting were devoted to the discussion of a case study and - based on additional material - to a more in-depth discussion of the problems and dilemmas of study methods in complementary medicine. The first part of the discussion of practical examples was devoted to the method of *acupuncture*.

4. Methodological Approaches: Examples in Practice I

Speaker:
Dr. Claudia Witt, Charité University Medical Center

Claudia Witt presented the results of a study of the efficacy of acupuncture. This study was carried out in the Institute of Social Medicine, Epidemiology, and Health Economics at the Charité University Medical Center in Berlin. In her presentation she compared different primary outcomes and statistical methods and how they could influence the interpretation of study results. The aim of her study, which she used as an example, was to evaluate if acupuncture was more effective than sham acupuncture (12 sessions in each group). The randomized controlled single blind trial included patients with low back pain between the ages of 40 and 75. The predefined primary outcome was the change in pain intensity (visual analogue scale: VAS) after 8 weeks (difference baseline to 8 weeks). As predefined statistical analyses she used the student-t-test. She observed no significant differences between the acupuncture and minimal acupuncture groups. On contrary when comparing the means of both groups on the VAS after 8 weeks by using t-test there was a significant difference between both groups. However, when employing ANCOVA (adjusted for baseline values) as a statistical method for the same parameter she found a non-significant trend. Using 50% responder rates as primary outcome would also have resulted in a significant difference between acupuncture and sham acupuncture groups. The size of the specific effect in this study was classified as small. Witt mentioned that the results of studies are mainly interpreted according to significance, but that statistical significance does not say anything about the relevance of an effect.

According to Witt's example, the classification of a study as a negative or positive trial could be influenced by the choice of the outcome, the statistical analysis as well as the sample size. Therefore for studies in which only a small specific effect will be expected the primary outcome and statistical test should be well planned.

In the previous discussions it had already become evident that there is no common idea about the performance of CAM studies. Claudia Witt's paper and the **discus-**

sion following confirmed this fact. For example, it dealt with the details of the measurement of efficacy of acupuncture studies. The effect size and its interpretation was debated, as well as the problem of different statistical methods. There were difficulties in interpreting the consequences of Witt's results and the discussion again provoked criticism of study designs and the measurement of efficacy of CAM treatment. One general important point was raised, when researchers were asked to explain their statistical methods in a way that every non-statistician can understand them. Remarkably, besides criticism, again the importance of the context of clinical CAM studies was pointed out . But these studies should consider diseases who are normally treated by CAM methods and reflect the special context of patient-clinician interaction.

5. Comments and Discussion: The Dilemma of Study Methods in Complementary Medicine

Speakers:
Professor Dr. Karl-Heinz Jöckel, University Duisburg-Essen, Institute for Medical Informatics, Biometry and Epidemiology
Dr. George T. Lewith, University of Southampton, Complementary Medicine Research Unit

The following session went further in the critical discussion of clinical CAM trials. Two different viewpoints were taken into consideration. **Karl-Heinz Jöckel** dealt with the topic as specialist of informatics, statistics and biometrics. **George Lewith** gave a comment on the basis of his experience as a researcher and complementary medical practitioner.

Karl-Heinz Jöckel's starting point was a description of the expectations one should have in connection with managing clinical research. Different steps need to be considered if one wants to achieve meaningful study results in the end. These steps range from transforming a research question into a scientific research hypothesis to the proper and rigorous interpretation of the results. This kind of research management is essential for conventional medicine as well as for CAM. The ability of conventional medicine and CAM to take these two steps was compared, namely: (1) How a research question is transformed into a scientific hypothesis, and (2) how concepts are developed for deriving empirical data to refute or to verify the research hypothesis. In respect to the research question, the main difference between conventional medicine and CAM would be that the former would follow basic research as the leading principle in the acquisition of knowledge, whereas the latter would be "based on a theory inherent to complementary medicine". Concerning the concepts to derive empirical data, conventional medicine would rest on elaborate randomized trials, whose participants, together with their reaction to treatment, are assumed to represent all human subjects. In contrast to this "non-individualized" therapy, CAM would not have such a tool, but would rather focus on "individualized therapy". Jöckel pleaded for an alignment of both

approaches. This aim could be reached when developing methods applicable to conventional medicine as well as CAM.

Whereas Jöckel concentrated on the improvement of clinical trial methods within the frame of the well-known range of conventional tools and techniques, **George Lewith** questioned the overall importance of current routinely-applied study designs. He went back to the basic question "What evidence do we need?". Is it "efficacy", "effectiveness" or "cost effectiveness"? To analyze the impact of CAM, Lewith suggested evaluating CAM in practice as a "whole system". This approach could be exemplified with the case of acupuncture. The first question here would be to clarify what acupuncture is. There are different acupuncture techniques and control procedures. These include "real acupuncture [Traditional Chinese Acupuncture or Western Acupuncture]" and "sham acupuncture" which may or may not involve skin penetration. In this context, the large-scale German studies in particular were questioned as they viewed acupuncture as a single monolithic entity. In contrast one needs carefully detailed studies of the different methods. This is the only way to clarify whether acupuncture works or not. In the context of such studies it is important to consider both the non-specific effects and the duration of the study, as the clinical impact of treatment may increase when evaluated over the long term. Patient perceived benefits of acupuncture do exist and are often difficult to quantitate in RCTs using standardized outcomes. It is therefore always possible to explain the efficacy and effectiveness of the intervention with an approach which only investigates the relationship between predefined and poorly understood specific and non-specific effects. The doctors and the patients views and – last but not least – a qualitative evaluation of the patients systematic story are essential parts of any coherent research strategy. It is difficult to investigate the specific physiological mechanisms of acupuncture. Even if they are investigated, we are not sure whether this would explain efficacy. Lewith suggests concentrating much more on research evaluating the patients expectations with the help of approaches such as brain imaging techniques (functional MRI). Patients' expectations might explain the importance and meaning of non-specific effects, which could be fueled by these treatment expectations. Finally, Lewith again spoke in favor of the analysis of the context of CAM (e.g. patients, safety, and economics). Such a broad analysis should include the patient's help in designing trials (e.g. pelvic pain and endometriosis).

The **general discussion** which followed concentrated on the future design of clinical CAM studies. In the foreground of the debate stood Lewith's approach. Similar to the general discussion of the very first session of the conference, the idea of contextual research fascinated the participants. It seems clear that broad-scaled studies as suggested by Lewith need careful and long term preparation. This also means developing the confidence and intellectual capacity to carry out the studies. Research projects need to grow from the passion and ideas of the CAM research community. One needs interdisciplinary groups in high profile departments with good academic reputations. Such groups should work locally and nationally to create consensus and momentum. Networks for specific diseases need to be cre-

ated and there should be interaction between these networks. Topics worth study and focus should be chosen, e.g. pain and cancer. In the course of such studies it is important to be open to the different processes going on, e.g. the physician-patient relationship, and to consult different experts to investigate the application and outcome of CAM interventions. This could mean measuring patient empathy and empowerment as well as 'stress' and vegetative state. Many conventional medicine interventions are not evidence-based and/or based on individual case studies. The costs of such broad scale studies within the current research framework are a disincentive, but this problem also exists in conventional medicine. One has to convince sponsors about the importance of such new research strands. In the UK this is mainly done by "The Welcome Trust", the Department of Health, the Medical Research Council and a number of independent research charities. In Germany, except for charities such as the Karl and Veronica Carstens-Foundation and the Robert Bosch Stiftung, the pharmaceutical industry and the German Research Foundation (DFG) have only started to fund CAM on a small scale. To convince funders, one needs well-placed publications and a funding track record but without funding this is a difficult mountain to climb.

6. Key Note Speech: "The Quality of Clinical Trials in Complementary Medicine"

Speaker:
Dr. Jos Kleijnen, Kleijnen Systematic Reviews Ltd.

In the course of the discussions which had taken place so far, a lot of skepticism was expressed about the suitability of conventional study methods for purposes of CAM testing. In the key note of the second session about examples in practice, **Jos Kleijnen** again came back to the importance of considering regular quality standards when talking about the quality of clinical trials in complementary medicine. The sound basis of clinical trials is important both for conventional and complementary medical trials. This basis rests on the same principles, namely those of EBM. Firstly, it is important to get the objectives of the study right and to formulate questions appropriate to the research target. These questions influence decisively the validity of studies. Important for the research group is to make sure that the studies internal validity (randomized groups of patients, comparable prognosis of the groups, study design appropriate to the therapeutic effect of interest, clear observation standards etc.) and external validity (general applicability of study design and outcomes to society) is guaranteed. Also, systematic errors (bias) need to be prevented. Systematic errors mainly occur as selection bias, performance bias and measurement bias. To consider these points in study design and, therewith, create validity is a decisive step to carry out successful RCTs. On the basis of these facts, there is no reason in carrying out different study types for CAM. This should be done only in exceptional cases, e.g. as a help for decision making processes. "Improving the meaning of the results of studies" is important for conventional medicine as well as for CAM. Especially in measuring non-specific effects, blinding is very important. On this basis there is also no indication

that CAM studies are of poorer quality than conventional studies. In this sense an article on the effects of homeopathy, published recently in the *Lancet,* was criticized by Kleijnen: There are no differences between homeopathy and conventional medicine in contrast to the result of the study, which says that homeopathy is not better than a placebo.

The following **discussion** concentrated on the question of the applicability of Kleijnen's theoretical approach to the practical needs and conditions of CAM studies. Is it more difficult in CAM studies than in conventional studies to recruit adequate patient numbers? Is blinding really necessary and is it possible to blind patients in every case? Is it really possible to assess CAM studies? Kleijnen claimed that, in principle, CAM and conventional medicine have the same basic problems of study design. Above all it would be necessary to give adequate explanations of the trials to the patient. It would be a challenge for the physicians to give this information carefully and therewith to ensure an effective recruitment. Also, Kleijnen pointed out that it is, in principle, advisable to consider blinding in studies of CAM as well as conventional medicine, although the necessity of the method would depend on the research question. Although Kleijnen admitted that the "perfect study" can't be carried out, he insisted that one should at least try to carry it out as well as one can.
One point raised in the discussion were differences between the UK and Germany: Whereas in the UK, conventional general practitioners recruit patients for CAM studies, in Germany this is done by CAM physicians and homeopaths. This means that there is a more general approach in the UK.

7. Methodological Approaches: Examples in Practice II

Speakers:
Dr. Andreas Michalsen, Kliniken Essen-Mitte, Department of Internal and Integrative Medicine, University Duisburg-Essen

Dr. Renatus Ziegler, Hiscia Institute, Department of Biostatistics and Methodology of Clinical Trials
Dr. George T. Lewith, University of Southampton

The intensive discussion on the theory of study design was again followed by a second session presenting practical examples to sort out problems of trials and continuing the brain storming on how to proceed with CAM study designs. This second case study session consisted of three talks which were devoted to the areas of homeopathy and naturopathy.

The examples presented by **Andreas Michalsen** dealt with the possibility to blind studies on the therapeutic use of leeches, on fasting and vegetarian diet in rheumatoid arthritis and with a trial of cupping in carpal tunnel syndrome. In all three areas the necessity appeared not only to focus on usual study parameters. In contrast, the vision and view of the patient, his outcome expectations, beliefs and lifestyle

need to be analyzed and studied in much more detail. In last consequence, Michalsen supported the argument already brought forward about new study designs taking account of the cultural context of patients. In case of leech studies, blinding is simply not possible as the patients see the leeches. Therefore, psychological parameters such as the degree of the patient's outcome expectations fueled by the therapeutic measure play an important role for the study assessment. If compared with the treatment of diclofenac for Osteoarthritis, the patient's expectations for experiencing pain relief are much higher than when treated with leeches. The other two examples given by Michalsen demonstrated that it is very hard to analyze the life style of patients which may be key to outcome, such as assessing fasting and adherence to a vegetarian diet. Michalsen mentioned that they could not perform randomized trials in their own clinic as they could not convince patients to participate. Efforts to investigate the relation of lifestyle and coronary disease were somehow disappointing. Problems, appeared in all three examples suggesting selection bias, unwillingness to be randomized, and ceiling effects. Finally, the talk of Michalsen pleaded for the "combined hospital approach", namely to integrate conventional treatments, CAM treatments and classical naturopathy to achieve the best results in patients and compare this with equivalent populations receiving conventional medicine.

Similar methodological problems were demonstrated by **Renatus Ziegler** for the case of mistletoe trials on cancer patients. Patients treated with a mistletoe preparation (Iscador) in addition to conventional cancer therapy were compared with a control group which was treated with conventional cancer therapy alone. Randomization caused difficulties because the well-informed CAM patients often insist on being treated with mistletoe. The drug is well known and application bears no risks. Also, blinding was (and is) impossible or at least questionable because it is nearly impossible to produce a pure placebo imitating mistletoe preparations. Ziegler then gave an overview on different randomized mistletoe studies on international level, each consisting of small patient groups. There are many reasons for the discontinuation of various studies. These were related to problems the physicians experienced as well as the patients; "Motivation" and "compliance" were often absent in both trial organizers and trial participants and slow recruitment served to compound these problems. To a certain extent the performance of prospective randomized controlled studies and controlled retrospective longitudinal cohort studies represent approaches that may help to resolve some of these issues. Ziegler suggested that different study designs could be used to complement each other, for instance perhaps performing studies in areas where there is no expectation associated with the use of mistletoe. In each instance "reduction of symptoms, side effects of conventional therapy (…) and quality of life" should be considered in addition to mere survival-rates or measurement of tumor growth or reduction.

George Lewith spoke about a study carried out in Southampton, UK, and dealing with a RCT of homeopathy and placebo in the case of allergies. After randomization, 242 patients were entered. They had been recruited from 38 general practices in Hampshire and Dorset. The patients' ages were between 18 and 55. Within this

group, 122 were treated with homeopathy, 120 were treated with placebo. In the homeopathy group, 22 patients withdrew from the study. In the placebo group this occurred in 19 cases. The reasons were “major protocol violation” (e.g. oral steroids), “self withdrawal, concomitant illness, exacerbation of asthma”. 101 patients in the homeopathy group completed the trial and the same number of patients of the placebo group. The patients were observed for 20 weeks. Clinical visits were carried out and diaries were kept. The blinded study could show that there were differences between homeopathic treatment and placebo treatment in case of VAS. This result was unaffected by the attitudes of patients and physicians. But as the mechanism of the efficacy of homeopathic treatment remains uncertain, homeopathy “requires meticulous studies with long follow-up”. Lewith spoke in favor of funding such studies which would allow general statements on the impact of homeopathic treatment. Again, he pleaded to study and analyze CAM “within a whole system” and to consider the cultural context of the patient.

The following **general discussion** focused very much on the following topics:

Recruitment of patients and the acceptance of the different CAM methods. It was debated whether patients really care about new publications in CAM. This is questionable and one can assume that even critical comments on specific CAM methods do not lead people to drop out of studies or routine treatment. Sometimes announcements of new treatments are considered positively by patients with little evidence and expectations are raised; this occurs for both CAM and conventional medical treatments. Again, it was pointed out that, because many people with experience of CAM are convinced of the benefit of their treatment it is difficult to randomize them for studies. Rainer Lüdtke mentioned that only 10 % of eligible patients would be willing to be randomized in his experience. This could be a specific German problem, because patients are recruited into trails by their CAM physicians. As a way out, George Lewith suggested carrying out recruitment from primary care units or general practices. Patients attending these units do not expect to be treated with CAM, which would make things much easier and create greater equipoise.

Special pilot studies on different areas of treatment. They should be carried out before CRTs are performed. This is especially important in analyzing non-specific effects of treatment. There is a lot of basic research still to be done in diverse fields of CAM particularly in case of homeopathy; e.g. the structure of water needs to be analyzed more intensively. The same is true for the problem of entanglement. Although difficult to carry out, this kind of research seems to be especially important for homeopathy as we have no clear explanation for many observed phenomena. This basic research needs to be embedded in study designs which consider the broad range of factors influencing the therapeutic setting, e.g. the doctor-patient relationship and the doctor as healing factor or the life-style of the patients. Although the latter can be hard to investigate comprehensively it is important to measure single parameters. The problem is that those patients who need to change their lifestyles (e.g. in case of coronary artery diseases) are not

willing to do so and often allow only restricted analysis. Whether CAM patients are much more willing to change their lifestyles than patients receiving conventional medicine is still an open question, although there are some studies on this problem which suggest they might be (e.g. Andritzky 1997).

Again two topics, which had been raised several times before were debated, namely the *lack of funding* and the *difficulties to publish CAM studies*.

The lack of funding. It was pointed out that homeopathy is difficult to analyze and that it is difficult to pin down specific therapeutic effects. Therefore, because of the prejudices against homeopathy such studies are rarely funded. In general the costs of treatment is a vital issue for insurance companies who may be able to fund further investigations (in Germany the *Gemeinsamer Bundesausschuß*).

The difficulties in publishing CAM studies. It was mentioned that especially large studies can be published in high quality journals with difficulty. It is also much easier to publish studies of acupuncture than homeopathy.

8. Study Designs and Methods

Speakers:
Rainer Lüdtke, Karl und Veronica Carstens-Foundation: Study Methods: A funder's perspective
Dr. Felicity Bishop, University of Southampton, School of Psychology: Qualitative Methods
Prof. Dr. Walter Aulitzky, Robert Bosch Krankenhaus: Randomized Double Blind Studies
Professor Dr. Eduard Stange, Robert Bosch Krankenhaus: Evidence Based Medicine - Evidence Grading
Prof. Dr. Stefan Willich, Charité University Medical Center, Institute for Social Medicine, Epidemiology, and Health Economics: Opportunities for Outcome Studies

In the last session of the conference, the participants again discussed the major topics raised at the start of the meeting. Five papers informed different study designs.

The “funder’s perspective” on study designs and methods was explained by **Rainer Lüdtke**. With an annual budget of 1.5 million Euro, the Karl und Veronica Carstens-Foundation aims at the “integration of homeopathy and naturopathy into conventional medicine”. Projects with different study designs are sponsored: RCTs, non-randomized trials and also outcome studies. The underlying assumptions of the foundation’s work are that it is possible to research intensively on CAM and that it is possible to integrate CAM into conventional medicine because physicians notice and apply respective methods. But these aims are difficult to achieve because of two reasons:

1. Conventional researchers are prejudiced against CAM. Lüdtke gave examples that the positive evidence of CAM studies had been ignored and down played. This is also true for CAM practitioners.

2. Application of the specific study designs overstrains researchers. The reasons are missing interest and poor training in adequate research methods to analyze CAM problems. Also, the methodological discussion is restricted on empirical methods, effectiveness, design matters and innovative suggestions tend to be viewed with suspicion. One of major points raised by Lüdtke was that in his view too much weight is laid on randomization as a core problem of study design. The challenge is to analyze the expectancy of the patients much more carefully with respect to individual CAM treatments and to integrate this knowledge into future study designs. The question "Is the perception of CAM correlated to the methodological quality of research?" needs to be answered.

Whereas Lüdtke concentrated on the problem of making CAM attractive to conventional medicine on the basis of an adaptation of conventional study designs to the needs of CAM studies, **Felicity Bishop** discussed to the appropriateness and value of qualitative research in CAM. With this paper, the necessity of a broad vision and approach to CAM study designs was discussed again. This topic, which was tackled in many of the conference participants' comments, was now presented in detail. Bishop discussed the underlying philosophical assumptions that can be a feature of qualitative research, namely that language and culture differs in social groups and individuals and there "is no value free, neutral, objective reality, that we know". Qualitative research concentrates on the analysis of language and culture, and is able to focus on "peoples' meanings and understandings" and on the "world contexts", on "everyday lives". A range of qualitative methods enable the systematic investigation of the socio-cultural context of CAM either within the context of RCTs or as stand-alone studies, e.g. interviews, participant observation, non-participant observation or open-ended questionnaires. The material acquired is analyzed not only on the basis of its contents, but there is also an interest in the ways in which language is used, and how this relates to the broader social context. The overall aim is to achieve insights into the patients' and the practitioners' perspectives. Several illustrations served Bishop in underscoring her argument that different qualitative methods and different combinations of qualitative and quantitative methods can be used to further our scientific understanding of CAM. One example is in the preparation of a patient questionnaire, in which qualitative methods of thematic analysis and "think aloud" can be used to inform the design and development of a quantitative questionnaire.
Finally, Bishop claimed to highlight a lot of issues still waiting for investigation and argued that qualitative research needs to be used more widely in order to enrich our knowledge of CAM usage and application. Above all she pointed out the importance of combining methods and exploiting the full range of options to perform adequate research.

Walter E. Aulitzky came back to conventional study methods when talking about randomized controlled studies. When creating a hierarchy of evidence, controlled studies still have priority, followed by observational studies, case series and case reports. Aulitzky then described the key elements of RCTs. After having reviewed ethical issues, the objectives need to be quantified and the study population needs to be defined. Thereafter, treatment and controls should be specified. Then the endpoints of the study need to be defined as well as the methods of assessment. The quantitative properties of the design have to be calculated, procedures for managing data should be established and finally treatment allocation and bias needs to be controlled. Aulitzky then concentrated especially on the placebo response as a significant marker to estimate the efficacy of CAM treatment. The response rates to placebos are often closely related to the response rates to treatment. This shows that the specific effect of all interventions is often very small and that in both cases the non-specific effects are dominating. In detail, the response rates to placebo depend on the disease state, the possible small effect of the placebo pill and a large non-specific effect caused by contextual conditions, which are measurable only with difficulty (communication with the physician etc.). Finally, Aulitzky concluded that one should search for specific effects of CAM to get evidence for efficacy. Also, it would be helpful if disease states with smaller non-specific effects of therapy would be analyzed. Last but not least the mechanisms of the efficacy of non-specific measures should be investigated more carefully.

The next paper ventured even deeper into conventional medicine. **Eduard Stange** focussed on EBM and therewith presented the third paper on the topic at this conference – but from the clinical point of view. The hierarchical conditions in EBM were criticized as some methods are more recommended than others. Also, different centers for EBM have different outcomes when evaluating RCTs. In general, the medical market is flooded with RCTs and meta-analysis studies and it is difficult to retain an overview. Remarkably, this is not a surplus of valid information, because there is the clear tendency not to publish negative results, e.g. those with a clear superiority for the placebo effect. This could be demonstrated with the example of acute Crohn's disease. For Stange, this is "Evidence B(i)ased Medicine": Quoting Melander (BMJ 2003), evidence being publicly available is biased by "selective publication, undisclosed duplicate publication and the tendency to publish only studies with positive findings". The involvement of the pharmaceutical industry is problematic, because industry-sponsored studies have a more favorable outcome than non-sponsored trials and at least 50 % of the trials performed are sponsored by the industry.

Finally, the opportunity and need for outcome studies was analyzed by **Stefan N. Willich**. The starting point of his talk was the crucial importance of potential confounders in research studies. Controlling for confounding means considering different contextual factors independently associated with exposure and outcome to achieve a valid evaluation of the outcome of studies. To neglect confounders may imply severe bias. Willich used the studies on hormone replacement therapy in

postmenopausal women as an example to emphasize his argument. Hormone replacement therapy was erroneously seen as a good choice to lower myocardial infarction risk, because the social context of the women had not been adequately assessed in observational studies. In an RCT the risks of hormone replacement therapy became apparent. RCTs are the appropriate standard in establishing efficacy. However, to base decisions as to medical strategies in general practice solely on RCTs is insufficient. Results of RCTs are often not helpful and often have an unclear relevance for routine therapy. Their strongpoint is mainly efficacy (clinical and pharmacological effect), whereas the investigation of effectiveness and efficiency is important to evaluate a therapeutic measure for clinical practice. The areas of effectiveness and efficiency are tackled by outcome studies. Therefore, they are very important. One recent example is the study program acupuncture by the *Techniker Krankenkasse* in Germany. Observational studies may provide insight into patterns of care, e.g. the treatment rate of hypertension investigated by the MONICA-Project in Augsburg/Germany. Willich suggested to conduct more outcome studies in association with RCTs, so-called "RCT-plus"-studies. The latter integrate, in his view, the evaluation of efficacy, effectiveness and efficiency. With his talk, Willich also gave support to all those who had raised their voices in the course of the conference in favor of a much deeper analysis of the cultural context of CAM.

The following **discussion** was dominated by three major topics, namely the relationship between CAM or CAM studies and conventional medicine, the problems with usual methods of conventional medicine and their evaluation and finally again the cultural context of CAM studies.

The relationship between CAM and CAM studies and conventional medicine:
During the discussion of Lüdtke's paper, his assumption concerning the resistance of conventional physicians and researchers was only partially confirmed. One major point of criticism was that blaming officials for stubbornness and demanding evidence would be counterproductive for CAM research, because many CAM studies do not rely on RCTs. 75 % of remedies would be lost if one had to rely solely on usual conventional study designs, a similar situation might occur with some of the older conventional medicine. Another point of criticism raised was that there should be no prejudice by officials within the registration agencies. Their own individual beliefs about CAM should not form a significant part of the process of registration. It was also debated as to whether patients along with their expectation should have more input into study design. It appears that with respect to study design and subsequent publication patient input may have a negative impact on the validity of studies.

The problems with usual methods of conventional medicine and their evaluation:
The participants discussed general problems to measure evidence and the meaning of the placebo effect for study evaluation. The latter needs to be seen not only as a negative factor which diminishes the efficacy of the treatment to be tested. The placebo effect could be also "the self-healing capacity of the body", which should

be provoked by the physician (Dobos). Again the meaning of RCTs was debated controversially as these trials do not automatically provide evidence for therapeutic efficacy. To carry out randomized outcome studies (ROS) might be one way to improve the situation.

Participants spoke in favor of independent research and independent studies. There should be cooperation between different institutions to bring an end to the bias created by the pharmaceutical industry (Aulitzky). Even the studies on medical technologies are biased. As the possibilities of funding by the German Research Foundation (DFG) are limited because its budget is unlikely to increase, researchers have to look for other sources, e. g. foundations such as the Robert Bosch Stiftung, insurance companies etc. Furthermore, it is important to get control over publications. Although EBM is important, it is necessary to consider all its limitations and to try to improve EBM measures in respect of CAM study designs.

The cultural context of CAM studies:
Several questions were raised as to how to perform qualitative studies as proposed by Bishop. As qualitative work is above all used in the UK, it was asked: How should we start with qualitative work in Germany? This might be done with interviews to acquire more knowledge about the patients' perspectives. Another tricky question concerned the possible qualitative methods to convince physicians that it is worth considering CAM therapies. The best way seems to be to combine different methods, which was proposed in the paper as the right way to proceed. An important issue raised was that quantitative work, the performance of statistics, rests on qualitative work. According to Bishop, only qualitative work tells us, why patients stick to specific recommendations, e.g. for back pain, and why they use a physiotherapist for a specific time. No clinical studies can tell us what is going on in the heads of patients.

9. Summary

Although a lot of different topics were discussed in the course of this meeting four core aspects were identified, which clearly dominated the conference. These aspects could be also used as a guideline or starting point for future discussions about CAM study designs.

There is no overall consensus on how to design CAM studies.
As expected, the sessions on the case studies and the following discussions showed that there were different opinions among all participants about CAM study design in general. The trial methods were debated controversially, as well as their scope, the range of expertise needed, who should be involved, and who should fund the studies.

Study designs of conventional medicine (RCTs) to be considered when planning CAM studies.

Although there was no unanimous agreement about study design and about the applicability of RCTs to CAM, there was a clear tendency to consider RCTs as option for future planning and to think about a further adaptation of RCTs to the needs of CAM. There was also the desire to bridge the gap between conventional medicine and CAM. Remarkably, EBM was seen as an approach, which does not necessarily correspond better to the needs of CAM than it does to conventional medicine.

CAM study design to remain flexible.
It became clear in the course of the meeting that CAM needs a variety of study designs to approach the diverse aspects and questions of the field. Flexibility is important, above all, because efficacy, effectiveness and effectivity of CAM studies cannot be investigated entirely on the basis of conventional methods. In contrast, evidence can be achieved only when using different approaches and methods to analyze the reasons, why patients use and adhere to CAM.

CAM study design to take into account the cultural context.
Whereas the three points described above tackled sometimes old and well-known problems the cultural aspects of therapeutics seemed to the participants a very promising approach for future research. This refers to the therapeutic content and expectations of the patients and physicians and the interaction between them both. This could help CAM find an explanation for the effectiveness of some CAM therapies, which might not be identified by biochemical investigation. Interdisciplinary work including proper representation of the academic humanities is vital.

10. Annex

List of Participants

Dr. Henning Albrecht	Karl und Veronica Carstens Stiftung, Essen
Prof. Dr. Walter Aulitzky	Robert Bosch Krankenhaus, Stuttgart
Prof. Dr. Ulrike Beisiegel	University Medical Center Hamburg-Eppendorf
Lilo Berg	Berliner Zeitung
Dr. Felicity Bishop	University of Southampton, School of Psychology, UK
Prof. Dr. Martin Dinges	Institute for the History of Medicine of the Robert Bosch Stiftung, Stuttgart
Prof. Dr. Gustav J. Dobos	Kliniken Essen-Mitte, Department of Internal and Integrative Medicine, University Duisburg-Essen
Corina Güthlin	University of Freiburg, Institute of Environmental Medicine and Hospital Epidemiology
Dr. Roman Huber	University Hospital Freiburg, Department of Internal Medicine II
Prof. Dr. Karl-Heinz Jöckel	University Duisburg-Essen, Institute for Medical Informatics, Biometry and Epidemiology
Prof. Dr. Robert Jütte	Institute for the History of Medicine of the Robert Bosch Stiftung, Stuttgart
Dr. Jos Kleijnen	Kleijnen Systematic Reviews Ltd, York, UK
Curt Kösters	Deutscher Zentralverein homöopathischer Ärzte, Hamburg
Prof. Dr. Karin Kraft	University of Rostock, Chair of Naturopathy
Dr. George Lewith	University of Southampton, Complementary Medicine Research Unit, UK
PD Dr. Klaus Linde	Technical University Munich, Center for Complementary Medicine Research
Rainer Lüdtke	Karl und Veronica Carstens-Stiftung, Essen
Dr. med. Andreas Michalsen	Kliniken Essen-Mitte, Department of Internal and Integrative Medicine, University Duisburg-Essen
Dr. Hans Peter Ogal	Aeskulap-Klinik Dr. Brander, Center for Clinical Holistic Medicine, Switzerland
Dr. Benno Ostermayr	Krankenhaus für Naturheilweisen, Munich
PD Dr. Cay Rüdiger Prüll	Albert-Ludwigs-University Freiburg, Institute for History of Medicine
Lars Broder Stange	Chairman Deutscher Zentralverein homöopathischer

	Ärzte, Kissing
Prof. Dr. Eduard Stange	Robert Bosch Krankenhaus, Stuttgart
Dr. Michael Teut	Health Center Polikum, Berlin
Prof. Dr. Stefan N. Willich	Charité University Medical Center, Institute for Social Medicine, Epidemiology, and Health Economics, Berlin
Dr. Claudia Witt	Charité University Medical Center, Institute for Social Medicine, Epidemiology, and Health Economics, Berlin
Dr. Renatus Ziegler	Hiscia Institute, Department of Biostatistics and Methodology of Clinical Trials, Switzerland
For the Robert Bosch Stiftung:	
Dr. Ingrid Wünning	Head, Science Department
Michael Schwarz	Program Officer, Science Department

Program

Thursday, 20 April 2006

12:30
Arrival and Snack

13:00
Opening
Dr. Ingrid Wünning, Robert Bosch Stiftung

Introduction of Participants

13:30
Introductory Remarks
Study Design and Methods:
The State of Present Knowledge
Dr. Klaus Linde, Technical University Munich
Dr. Jos Kleijnen, Kleijnen Systematic Reviews Ltd

14:30
Panel Discussion
Studies in Complementary Medicine:
Choice Methods - the Choice of the Method
Professor Dr. Walter E. Aulitzky, Robert Bosch Krankenhaus
Dr. Roman Huber, University Hospital Freiburg
Dr. Andreas Michalsen, University Duisburg-Essen

Moderation:
Lilo Berg, Berliner Zeitung

16:15
Coffee Break

16:30
Methodological Approaches
Examples in Practice I
Chairperson: Dr. Roman Huber

Short presentations of studies and their methodological problems
in the field of Acupuncture
Dr. Hans P. Ogal, Aeskulap Klinik Dr. Brandner
Dr. Claudia Witt, Charité University Medical Center

17:30
Comments and Discussion
The Dilemma of Study Methods in Complementary Medicine
Chairperson: Prof. Dr. Martin Dinges
Professor Dr. Karl-Heinz Jöckel, University Duisburg-Essen
Dr. George T. Lewith, University of Southampton

Friday, 21 April 2006

9:00
Key Note Speech
„The quality of clinical trials in complementary medicine“
Dr. Jos Kleijnen, Kleijnen Systematic Reviews Ltd

9:45
Discussion

10:15
Coffee Break

10:45
Methodological Approaches
Examples in Practice II
Chairperson: Prof. Dr. Karin Kraft

Short presentations of studies and their methodological problems
in the fields of homeopathy and naturopathy
Dr. Andreas Michalsen, University Duisburg-Essen
Dr. Renatus Ziegler, Hiscia Institute
Dr. George T. Lewith, University of Southampton

12:45
Lunch

14:00
Study Designs and Methods
Chairperson: Prof. Dr. Ulrike Beisiegel

Study Methods: A funder's perspective
Rainer Lüdtke, Karl und Veronica Carstens Stiftung

Qualitative Methods
Dr. Felicity Bishop, University of Southampton
Randomized Double Blind Studies
Prof. Dr. Walter Aulitzky, Robert Bosch Krankenhaus
Evidence Based Medicine - Evidence Grading
Professor Dr. Eduard Stange, Robert Bosch Krankenhaus
Opportunities for Outcome Studies
Prof. Dr. Stefan Willich, Charité University Medical Center

17:00
Closing Remarks
Professor Dr. Robert Jütte, Institute for the History of Medicine of the Robert Bosch Stiftung

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Impressum

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