





## **1 Preface**

As a homeopath and acupuncturist since 1985, time had come for me to face new challenges. After finishing my master degree in Tromsø 2010, I gladly took the opportunity to be a PhD student at the National Research Center in Complementary and Alternative Medicine (NAFKAM) department of Community Medicine at the University of Tromsø. The protocol for my application to NAFKAM was written with the support of Aslak Steinsbekk, who had developed the first version of the questionnaire (applied in paper VI) in January 2010, and in August 2010 I joined the center.

I would like to thank all my colleagues at NAFKAM for their friendship and support, and all my collaborators in the “Safety of Treatment Provided by the Homeopath” study for their excellent job during the study. Especially, I want to thank my supervisors Terje Alræk and Marja Verhoef for their enthusiasm, knowledge and kindness and for always being there for me. A special thanks to Frauke Musial, the research leader at NAFKAM, who provided me with good advice and supervision whenever I needed it, and Åsa Sohlén whose knowledge of layout and design, improved my figures and models substantially. Thanks to Jane Ekelund for help and advice during the writing process.

In addition, I would like to thank Agnete, Anita and Mona (the PhD student group at NAFKAM), for a lot of fun and solid discussions, and last but not least Vinjar Fønnebø for structural help whenever I needed it.

Above all, I want to thank my children, Jessica, Michael and Katrine Louise for their acceptance, and support of my idea and vision to sell my clinic and our house in order to move to Tromsø and do research on homeopathy. I want to thank my mother Ella and my sister Tove for always being there for me and for their financial support.

## **2 Abstract**

### *Introduction*

Homeopathic treatment has a long tradition. Because of its widespread use as alternative therapy in Norway and Europe, but also in nations such as India, investigation into patient safety related to homeopathic treatment is important. Risk in homeopathy can be divided into direct and indirect risk. Direct risk is directly linked to the intervention itself while indirect risk is related to the setting effects, such as e.g. the practitioner, rather than to the homeopathic remedy.

Homeopathic aggravation, a concept specific for homeopathy, may impose a particular risk as it allows the health status of the patient to deteriorate before there is an improvement. In homeopathic theory, such a temporary deterioration is seen as being a part of the healing process.

### *Aims*

In this research plan, adverse effect was understood as all diseases or unwanted and/or harmful reactions appearing during a study period, regardless of their relation to the actual treatment. The term encompasses all unwanted effects, without making assumptions about their mechanisms. It thus avoids ambiguity and the risk of misclassification.

The aim was to explore and provide more knowledge about patient safety in homeopathy. With regard to safety, particular emphasis was placed on the concept of homeopathic aggravation.

### *Materials and Methods*

A mixed method approach combining qualitative and quantitative methods was used, including four focus group interviews, a cross-sectional survey, a systematic review, and a meta-analysis.

### *Results*

Initial steps were taken towards development of guidelines for the assessment of risk in homeopathy. The results suggest that both lay as well as medical homeopaths assessed the patient risk precisely according to the guidelines developed in this research project. Adverse effects as well as homeopathic aggravations were reported by patients after homeopathic treatment.

According to the CTCAE criteria, these events were mild to moderate and transient. According to the systematic review and meta-analysis included in this research plan, direct risk related to the

homeopathic remedy was found to be minor and moderate, apart from five cases of homeopathic aggravations that were graded as serious. The meta-analysis suggested that adverse effects were reported to a similar degree in the homeopathy compared to the placebo groups.

### *Conclusion*

According to the systematic review and cross-sectional study included in this research plan, homeopathic treatment is generally associated with low to moderate direct risk related to the remedy. Indirect risk, however, is associated with homeopathic practice where the concept of homeopathic aggravations imposes a particular risk. To control for indirect risk and improve patient safety, it is important to distinguish between homeopathic aggravations and adverse effects within homeopathic theory. Criteria to distinguish these two concepts must, however, be acceptable to homeopaths and applicable in everyday practice. Furthermore, it allows comparison of safety data across studies on homeopathy. A reporting system for adverse effects in homeopathy should include criteria to distinguish these two concepts, among others, which enables homeopaths to apply this reporting system. Moreover, severity and duration of both homeopathic aggravations and adverse effects need to be classified within the same grading system. The criteria developed in the research plan presented here were tested and found relevant for safety purposes. In addition, it turned out that high medical and homeopathic skills are required to assess patient risk accordingly, which is heavily dependent on homeopathic training and education. Consequently, there is considerable potential for risk related to homeopathic practice due to the current, legal regulation of the profession.

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## **6 List of abbreviations**

CAM	Complementary and Alternative Medicine
CTCAE	Common Terminology Criteria for Adverse Events
GP	General Practitioner
ICPC-2	International Classification of Primary Care (ICPC-2)
MD	Medical Doctor
PICO	Population Intervention, Comparison, Outcome
RCT	Randomized Controlled Trials
RFE	Reasons for encounter
SR	Systematic Reviews
WHO	The World Health Organization

## **7 List of papers**

### **Paper I**

Stub T, Raak C, Ostermann T, Musial F, Alraek T, Adverse effects of homeopathy, what do we know? A systematic review and meta-analysis of Randomized Controlled Trials. BMC Complementary and Alternative Medicine. Submitted in December 2013.

### **Paper II**

Stub T, Salamonsen A, and Alraek T, Is it Possible to Distinguish Homeopathic Aggravations from Adverse Effects? A Qualitative Study. Forschende Komplementärmedizin/Research in Complementary Medicine, 2012. 19(1): p. 13-19.

### **Paper III**

Stub T, Alraek T, and Salamonsen A, The Red Flag! Risk assessment among medical homeopaths in Norway: A qualitative study. BMC Complementary and Alternative Medicine, 2012. 12(1): p. 150.

### **Paper IV**

Stub T, Kristoffersen A, Alraek T, Musial F, Steinsbekk A, Risk in Homeopathy: Classification of Adverse Effect and Homeopathic Aggravation – A Cross Sectional study among Norwegian Homeopathy Patients. BMC Complementary and Alternative Medicine. Re-submitted in December 2013.

## 8 Definitions of terminology used in the thesis

**Adverse drug event** is harm caused by the use of a drug. In common practice it may be defined as harm caused by a drug or the inappropriate use of a drug.

**Adverse drug reaction** is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product. The reaction predicts hazards regarding future administration and warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

**Adverse effect** is understood as all diseases or unwanted and/or harmful reactions resulting from a medication or an intervention, regardless of their relation to the actual treatment.

**Adverse event** is any unfavorable and unintended signs (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Adverse event is an incident (event, circumstance, complaint and loss) in which a person receiving health care is harmed. *Event* is understood as something that happens to or with a person.

**Adverse reactions** are present when the right drug was administered for the correct indication, in the proper dose, by the right route, yet still the patient develops an unwanted symptom, suffers unexpectedly, and is exposed to unpreventable harm. Adverse reactions may also result from some diagnostic tests, therapeutic interventions or devices.

**Alternative treatment (CAM)** is primarily understood as health-related interventions practiced outside the official health care system by unauthorized health personnel. Moreover, treatment practiced within the official health services or by authorized health personnel is also covered by the term alternative treatment if the methods are essentially used outside the established health services.

**Homeopathy/homeopathic treatment** is everything a homeopath does in the consultation, from prescribing homeopathic remedies to giving other kinds of alternative treatment and lifestyle advice. An important element of the therapy is the particular interaction between the patient and the homeopath due to long consultation times.

**Homeopathic aggravation** is a temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription, which is expected to be followed by an improvement.

**Classical homeopathy** is a system of medicine using substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients.

**Medical error** is commonly defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health care professionals, patients or consumers.

**Nocebo** is the development of negative effects that are attributed to a medication, albeit the drug itself does not cause the provocation of these symptoms.

**Placebo** is a harmless pill, medicine, or procedure prescribed more for the psychological benefit to the patient than for any physiological effect. The *placebo effect* refers to any improvement of the condition of an individual who has received a placebo treatment. It is assumed that, if the placebo had not been given, no such improvement would have been observed. In contrast, *placebo response* refers to the change in an individual caused by a placebo manipulation.

**Patient safety** is the reduction of risk of unnecessary harm associated with health care to an acceptable minimum, understood as preventing and limiting unfortunate consequences or damages due to any health treatment.

**Risk** is a compound measure of the probability of an event, and the magnitude and impact of its potentially negative outcome of that event.

**Direct risk** is related to the intervention, e.g., harm caused by pharmacological products, medical treatments and procedures.

**Indirect risk** is related to the setting effects, such as the practitioner rather than to the medicine. For example, a practitioner with limited medical and homeopathic skills may overlook serious symptoms and thereby cause a delay in necessary conventional treatment.

**Side effect** is an effect produced by an agent, other than that intended.

**Surveillance** is the process applied to collect, manage, analyze, interpret and report health information.

## 9 Introduction

### 9.1 The principles of patients' rights and patient safety

Patient safety in homeopathy was the main focus in the research plan presented in this thesis.

Historically, risk and patient safety have been considered essential in treatment since the time of Hippocrates and the dictum to *do no harm* has been imperative (1). With the dramatic advance of the medical profession over the last fifty years, the topic has received considerable attention, in particular with the introduction of “The Nuremberg Code” (2), and the Helsinki declaration (1964/2004) in medical research.

A severe example from homeopathic treatment in which the ethical dictum *to do no harm* was heavily violated, was a case where a 9 month old baby was admitted to hospital after homeopathic treatment (3). She had been given several homeopathic remedies to treat atopic dermatitis. The child developed Bullous Pemphigoid during the treatment period, which lasted for five months. When the baby was finally admitted to hospital, its condition was life threatening. This severe situation occurred because the homeopath interpreted the worsening of symptoms as homeopathic aggravations and continued treatment instead of referring the baby to conventional care (figure 9-1). This case illustrates that even though homeopathy is regarded by many as a non-effective and harmless intervention, homeopathic practice, even though many patients utilize it with high satisfaction (4, 5), may not be entirely risk free.

Homeopathy was established and developed in Germany in the late 18<sup>th</sup> century by Samuel Hahnemann. *Classical homeopathy* is “a system of medicine using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients” (6). The practice of homeopathy involves the selection and prescription of a single remedy that is prescribed in a dosage expected to improve the patient's symptoms. As the mechanisms of the action of homeopathic remedies remain unclear, this form of treatment is controversial and considered to lack evidence.

*Homeopathy* in the context of this dissertation is understood as everything a homeopath does in the homeopathic consultation, from prescribing homeopathic remedies to giving other kinds of alternative treatment and life style advice. An important element of the intervention is the particular interaction between the patient and the homeopath. As a general rule, patients

consulting homeopaths often receive additional advice on life style issues. Some of them may be related to the homeopathic theory, e.g., not to drink coffee. Other types of advice are usually based on the knowledge of the individual homeopath. Moreover, most homeopaths expect a certain degree of worsening in the symptoms throughout the intervention, meaning that the health status will deteriorate before improving, and inform their patients about this expectation. This expectation relates to the concept of homeopathic aggravation which is a part of homeopathic theory and describes a temporary deterioration of the patient's health status, followed by an improvement (7) (For further discussion see section 11.4).

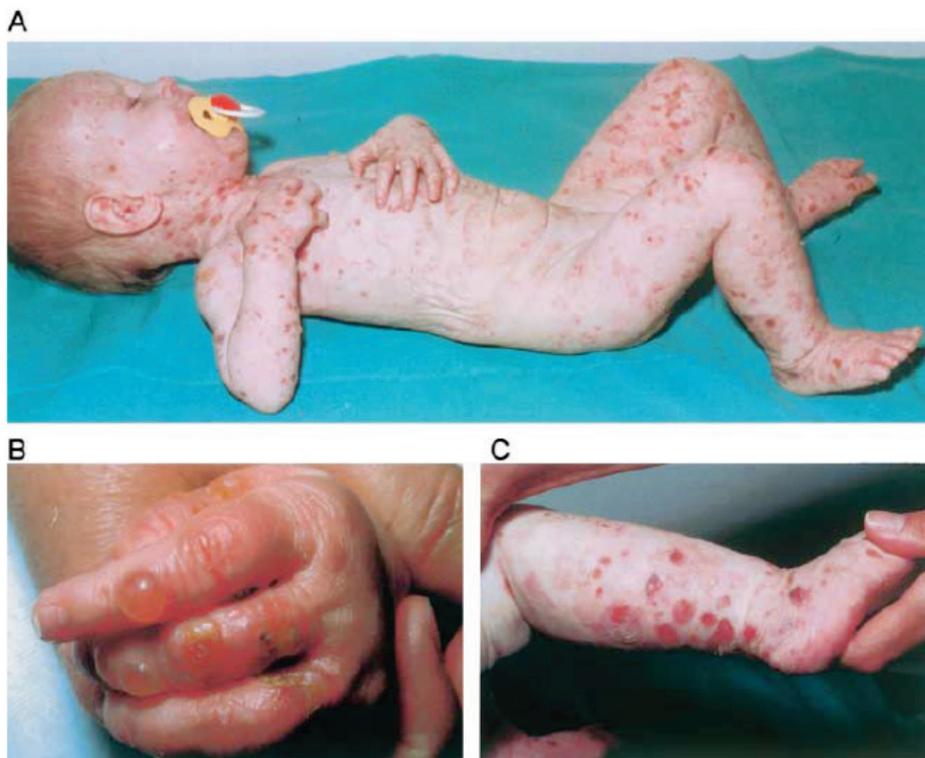


Figure 9-1 Baby with generalized tense blisters, erosions, and crusts. Lesions also affect the face, hands and feet. (A) Note the lack of subcutaneous fat and sign of dehydrations, with skin hanging in loose folds and the abdomen and trunk. Close-up view of the lesions on the (B) left hand and (C) right leg.

Basically, four ethical rules are fundamental with regard to patients' rights: 1) *Non-maleficence* or the duty not to harm patients, meaning that the harm should not be disproportionate to the benefits of treatment, is one of Beauchamp and Childress' widely accepted four major ethical principles in the medical profession (8). 2) *Beneficence*, understood as the importance of balancing the benefits of treatment against the risks and costs. 3) *Respect for autonomy*, emphasising the significance of respecting the decision-making capacities of autonomous

persons. This principle enables individuals to make reasoned, informed choices. 4) *Justice*, expressing a fair distribution of benefits, risks and costs, and the idea and concept that patients in similar situations should be treated in a similar manner.

To avoid unnecessary risk to patients during treatment is therefore a basic ethical principle and the operationalization of that principle is to ensure patient safety. With regard to this research plan, two definitions of patient safety were regarded as appropriate: Patient safety was understood as the reduction of risk of unnecessary harm associated with health care to an acceptable minimum (9). Furthermore, the definition by Aase et al (10) who define patient safety as preventing and limiting unfortunate consequences or damages due to any health treatment was considered essential.

Operationally and methodologically, risk is generally defined as a compound measurement of the probability of an event and the magnitude of the potential negative outcome of that event (11). Risk can be assessed from a variety of perspectives. In medical science risk can be divided into direct and indirect risk as illustrated in figure 9-2. Direct risk is caused by the treatment itself and related directly to the intervention, while indirect risk is related to the setting effects, such as e.g., the practitioner rather than to the medicine (12). For example, a practitioner with limited medical and homeopathic skills may overlook serious symptoms and, thereby, cause a delay in necessary conventional treatment, which is risky for the patient. A harmful reaction implying risk to patient safety is usually named “adverse effects” (13).

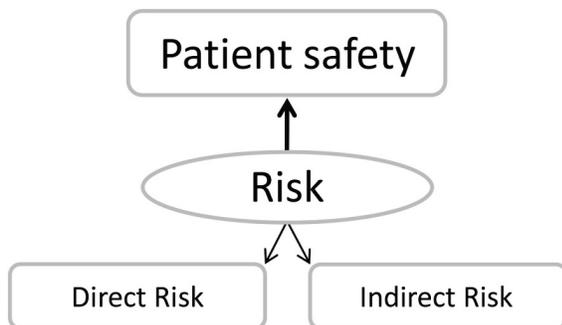


Figure 9-2 Understanding of patient safety and risk in this research plan. Direct risk is caused by the treatment itself and related directly to the intervention, while indirect risk is related to the setting effects, such as e.g. the practitioner, rather than the medicine.

## **9.2 Homeopathy as CAM treatment in Norway**

In the research plan presented here alternative treatment (also named Complementary and Alternative Medicine- CAM) is primarily understood as health-related interventions practiced outside the official health care system by unauthorized health personnel (14). Moreover, treatment practiced within the official health services or by authorized health personnel is also covered by the term alternative treatment if the methods are essentially used outside the established health services. For example, if an acupuncturist offers acupuncture at a private clinic she or he is an alternative practitioner. If a physiotherapist practices acupuncture inside a hospital, the treatment is defined as alternative treatment delivered as a part of her or his appointment as a physiotherapist.

As a general rule, therapies out of the spectrum of CAM are generally offered outside the National Health Care System in Norway, which may in itself be a risk to patient safety. Moreover, CAM therapies are usually derived from traditional systems of medicine (15), with little or no research tradition. Therefore there is often limited knowledge about efficacy, effectiveness, biological mechanisms, and safety issues and patient safety is a central and yet a widely unresolved issue in CAM. Consequently, the National Research Centre in Alternative and Complementary Medicine (NAFKAM) developed a research strategy with particular focus on patient safety (16).

Homeopathic practices are vaguely regulated in Europe and in Norway. Anyone, irrespective of training and regulation, can call himself or herself a homeopath. Consequently, homeopaths without appropriate medical and homeopathic training may fail to see and identify a severe health condition of the patient and may continue homeopathic treatment, even when conventional treatment should be imperative (17).

On the background of the current legal situation in Norway, the investigation of patient safety in CAM generally, and in homeopathy in particular is of primary importance. From the health authorities' point of view, it is of interest to know to what extent the therapy is used in society and to gather information about the likelihood of harm to patients when using it. From the patients' point of view, it is of high relevance to know whether the therapy is safe to use and whether it will help to improve health and/or reduce the symptoms. Therefore, similar to General Practitioners (GP), homeopaths are confronted with various kinds of conditions, from minor

complaints to severe, acute or chronic diseases. In order to ensure patient safety under these conditions, it is mandatory that homeopaths have medical knowledge not only about the limitation of the intervention itself, but also about the unfavourable effects that the treatment may cause in certain situations. Consequently, the Norwegian Parliament (The Storting) (18) requested differentiation between qualified and unqualified practitioners of alternative medicine. (Refer to the Norwegian Parliament's unanimous resolution in processing their parliamentary report "St. m. 50 1993-4 Samarbeid og styring".) The research plan presented here will focus exclusively on the risks to patient safety associated with homeopathic practice.

Within the framework of physiological and pharmacological knowledge, there is no plausible mechanism of actions for homeopathic remedies of high dilutions, since they are ultra-molecular and no molecule of the original substance is left in the remedy. This is one of the major reasons why homeopathy is rather controversial within the medical profession, and claimed treatment effects are commonly attributed to unspecific mechanisms or interpreted as pure psychological or placebo effects (19). Homeopathy is mostly controversial because, in this context, the remedy can be seen as a *ritual* of administering treatment and as such a part of the interaction between the patient, practitioner, and treatment environment. In such an interpretation, *the healing* would be a result of the clinical encounter (20). Considering the long consultation time the homeopaths offer their patients, and the intensity of the homeopathic anamnesis, it must be acknowledged that a placebo effect induced through increased attention is likely to play a relevant role in homeopathic treatment. However, a powerful effect as the placebo effect may also include aspects of harm to the patients, namely, if a *nocebo effect* is induced (21).

### **9.3 Risk in medicine**

#### **9.3.1 What is risk?**

*Risk management* in health care can be understood as designing and implementing a program of activities in order to identify and avoid or minimize risk to patients, employees, visitors, and institutions (22). In order to achieve these goals, an operational definition of risk is mandatory.

With regard to medical interventions, any pharmacological substance capable of producing a therapeutic effect can also produce unwanted or adverse effects. This holds true even for placebo and nocebo effects (for discussion see section 11.3.1). The risk related to these effects ranges from close to zero (for example the use of Nystatin) to high (the use of antineoplastic drugs) (23).

Studies indicate that adverse events occur almost daily in medium-sized hospitals or outpatient panels (24). Findings from Denmark (25), New Zealand (26), and Canada (27) suggest a relatively high rate of 10% adverse events (28).

Under the code of medical ethics, physicians are obligated to report adverse effects. However, voluntary reporting is often neglected and there are no individual consequences for not reporting adverse effects. Thus, the extent of underreporting remains unknown (29). Studies have shown that there is a tendency in the medical literature to underreport adverse effects in medicine. According to Venulit (30), only 21% of 1379 publications in conventional medicine contained adequate information to determine causality regarding adverse effects, most of which did not include sufficient information to interpret the clinical significance of adverse effects. A recent study confirmed these findings (31).

### **9.3.2 Different forms of risk**

In order to enable inclusion of as many risk aspects as possible, risk was defined broadly in the research plan presented here. As already pointed out, risk in this context is understood as a threat to patient safety and can be divided into direct and indirect risk (see figure 8-2).

It is likely that most simple “direct risks” (at least on a theoretical basis) are related to the intervention, e.g. such as harm caused by pharmacological products, medical treatments and procedures. Several terms are used to describe direct risk, such as adverse effects or adverse reactions, and adverse drug reactions. Moreover, numerous terms are used to describe adverse effects such as adverse reactions, adverse drug reactions and adverse events (9). In a survey 14 definitions were found for “adverse events”, 16 for “medical errors”, and five for “adverse drug events” (9, 22). These differences in definitions and the broadness of the contexts illustrate that risk in relation to a medical intervention is a complex problem and thus difficult to operationalize due to the inconsistent use of terminology.

In order to understand the complexity of the risk phenomenon, it is useful to elucidate the topic from different angles. Therefore, the following chapter will introduce several definitions of risk, which usually relate to different sources of risk and various conditions of its occurrence (the actual definitions are listed at paragraph 8). Table 9-1 summarizes the concepts discussed.

Table 9-1 Descriptors of risk grouped according to sources and concepts of risk.

<b>Risk Concept</b>	<b>Sources of risk</b>	<b>Descriptors/Origin</b>
Direct and indirect risk	Medical error (see section 9.3.2.1)	Human resources
Direct risk	Direct drug reaction (see section 9.3.2.2)	Adverse event Adverse drug reaction Adverse drug event Side effect
Direct and indirect risk	Comprehensive definitions (see section 9.3.2.3)	Adverse reactions Surveillance Adverse effect

### **9.3.2.1 Medical error**

A medical error (32) may occur from incorrect actions (commission) or failure to perform proper actions (omission) (22). Fortunately, the chance of a serious mistake occurring during any given medical procedure is small, but these errors happen. Philadelphia News reported several case histories about medical errors. One case involved a doctor performing brain surgery on the wrong side of a patient's head and another patient died after he had received an intravenous solution containing heparin (a blood thinner), 11 times the prescribed dose (33). Such events may be related to professional practice, health care products, procedures and systems, including prescriptions, order communications, product labeling, packing and nomenclature, dispensing, distribution, administration, education monitoring and use. Some authors estimate that less than 1% of medical errors result in harm (34).

### **9.3.2.2 Direct drug reaction**

A common term describing risk associated with direct drug action is **adverse event** (9, 35-37). It is recommended that the term adverse event is used in order to describe harmful events occurring during a trial (35, 38). An **adverse drug reaction** is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product. The reaction predicts hazards with regard to future administration and warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (23). Consequently, an adverse drug reaction is an adverse event with a causal link to a drug (32). An **adverse drug event** (39), however, is understood as harm caused by a drug or the inappropriate use of a drug (32).

When classifying adverse drug events, the first step is to find possible relations between the unwanted events and the medicinal products (including over-the-counter formulations, herbal and traditional remedies, recreational drugs or drugs of abuse). The next step is to determine possible

relations to the medication. In cases of patients taking several medicines, determining possible causative relations might be challenging. The problem is complex, since the cause of patients' complaints may be related to other, concomitant diseases, or one or more drugs or interactions between drugs. Therefore, the application of formal methods to assess the probability of cause related to a suspected drug event is common (40).

A **side effect** is an effect produced by an agent, other than that intended (22). However, this definition has been criticized since it is quite related to the immediate drug reaction and may therefore be interpreted as minimizing the potential hazard of the pharmacological product (agent). All of the above-described definitions are closely related to drug or pharmacological effects (direct risk). These definitions are useful when investigating or documenting direct risk, but they may underestimate the total risk of an intervention, since they exclude unwanted effects that are related to other aspects of the interventions (indirect risk). The following paragraph introduces a number of definitions that go beyond the immediate drug related phenomena, even though they include them.

### **9.3.2.3 Broader definitions of risk**

**An adverse reaction** is a broader definition of risk as it includes response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (22, 37).

In **surveillance**, the primary aims are to monitor the incidence or prevalence of specific health problems, to document their effects in defined populations, and to identify people and those at the greatest risk. The detection of an increase in health problems should alert health agencies and induce further investigation (41). Surveillance represents in this sense more a methodology than definitions. It is, however, interesting with regard to risk assessment, since it intends to explicitly monitor risk comprehensively and thus includes more sources of risk than merely those related to drugs.

**Adverse effect** (42), is quite similar to adverse event. However, an adverse effect is an adverse outcome that can be attributed to some action of a drug or an intervention, while an adverse event is a harmful event that occurs while a patient is taking a drug, for example during a trial. The term "adverse effect" encompasses all unwanted effects, without making assumptions about their mechanisms. Thus, adverse effect avoids ambiguity and the risk of misclassification (23).

Therefore, adverse effect covers, similar to surveillance, a broad spectrum of potential risks and thus includes more sources of risk than merely those related to drugs. However, compared to surveillance, the connection to the operational methodology is not as close.

### 9.3.3 “Adverse effects” as an operational definition of risk

A broader definition of risk is more appropriate in complex treatment situations, e.g. in rehabilitation or complex lifestyle oriented intervention programs. Such programs may be found in cardiology or diabetes care, where other interventions such as nutrition or physical exercise play a significant role besides appropriate medication.

The homeopathic intervention is a complex treatment situation that consists of in-depth consultations often reaching beyond the bodily complaints and that involves psychological problems. Moreover, this kind of intervention is generally combined with lifestyle advice. Consequently, a broader definition of risk is needed (see figure 9-3). Therefore, the term “adverse effect” that encompasses all unwanted effects, without making assumptions about their mechanisms is suitable for complex treatment situations like homeopathy.

#### Adverse Effects

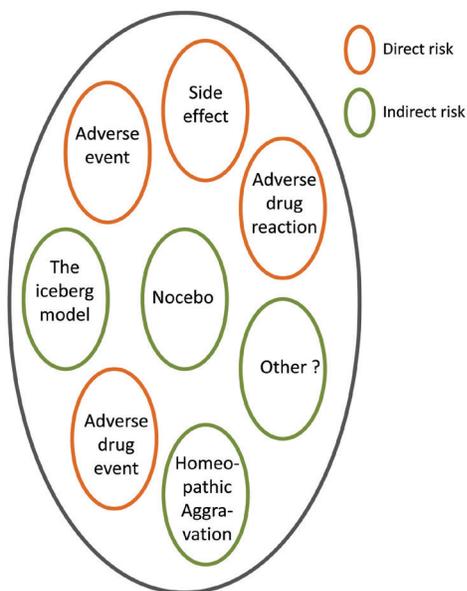


Figure 9-3 “Adverse effect” covers a broad spectrum of potential risks and thus includes more sources of risk than merely those related to drugs, and is therefore suitable for this research plan. This figure illustrates risk concepts categorized according to direct and indirect risk.

The nocebo effect is development of negative effects that are attributed to a medication, even though the drug itself does not cause the provocation of these symptoms. The iceberg model is a model of missed diagnosis. These potential risks will be further discussed later in the thesis (see section 11.4).

## **9.4 Risk in homeopathy**

### **9.4.1 Utilization, theory and practice of homeopathy**

Homeopathy is a popular treatment modality in Europe. The CAMbrella report found that homeopathy was used by 15% of the Europeans seeking CAM treatment (43). The most recent Norwegian study, conducted in November 2012, stated that 46% of the adult population had reported use of CAM during the previous 12 months. Thirty-seven percent had seen a CAM practitioner. The use of homeopathy was reported by 3% (44).

As mentioned earlier, homeopathy is not a part of the official health care system in Norway. The profession is vaguely regulated by the law of alternative therapies (14), which enables all citizens to legally treat patients as long as they cause no harm. Therefore, anyone can call himself/herself a homeopath regardless of education or training in homeopathy. The legal situation for homeopaths in Europe is mostly similar to Norway, with the exception of Switzerland, Latvia and Liechtenstein that have regulations of the profession as well as the treatment (45). Overall, 21 countries have vague regulations of the profession such as Norway, whereas 14 countries have no regulation of the profession or treatment (45).

Norway has a governmentally established registry for alternative practitioners. The registration is voluntary, but a membership allows the homeopaths to use the designation “registered” as supplement to their professional title. In order to obtain membership in the registry (Brønnøysundregisteret for alternative behandlere) the practitioner must prove to be a member of a professional association of practitioners, which has been granted official recognition from the registry. The purpose of the registry is i) to contribute to patient safety and consumers’ rights and ii) to enhance professionalism among registered alternative practitioners. However, there are no requirements regarding medical or homeopathic education for the practitioners in order to obtain membership in the registry. Moreover, there are only few physicians certified as homeopaths (medical homeopaths). Among the 1,151 Norwegian physicians who participated in a survey in 1997, only 46 practiced homeopathy (46).

According to homeopathic theory, the development of homeopathic remedies is based on two principles: i) the Law of Similiaris (*similia similibus curentur*), meaning “like cures like” and ii) individualization (7, 47). The hypothesis of the Law of Similiaris implies that substances capable of causing certain symptoms in healthy subjects can be used as medicines to treat people suffering from similar symptoms. Homeopathic medicines undergo a process of a stepwise dilution and vigorous shaking, until the content of the substance to be diluted is very low or non-existent in the solvent (alcohol, milk, sugar, or other) (48, 49). Avogadro’s number ( $6.023 \times 10^{23}$ ) is the threshold, indicating that no molecule of the original substance is left in the remedy. Such diluted remedies, which no longer include substrate, are called ultra-molecular (48). Homeopaths believe that *information* passes from the diluted agent to the solvent during the dilution process, which in light of current knowledge of physics is implausible. Since these remedies do not contain any *active substances* in a chemical or pharmacological sense, they could also be seen as pure placebos. Pure placebos, such as sugar tablets and saline injections (50) are inert treatment. From this perspective, homeopathy could be considered a pseudo-therapy.

However, not all homeopathic remedies are ultra-molecular. Many are low dilutions (D6 or D12). These remedies still contain a substantial number of molecules. Therefore, a direct pharmacological effect of the remedy in low dilutions is principally possible, whereas this is impossible for remedies of high dilutions.

In conclusion, while low dilutions may induce direct risk, any risk related to the administration of remedies of high dilutions must, according to current scientific knowledge, be related to indirect risk. Nonetheless, many patients report substantial benefits from homeopathic treatment (4, 51), even though ultra-molecular homeopathic remedies cannot be associated with pharmacological effects. Therefore, the homeopathic treatment with regard to ultra-molecular remedies may work via psychological mechanisms such as the placebo effect (19). Like in all forms of medicine, it is equally important to establish a good relationship with the patients in order to understand and interpret the patients’ symptoms. The particular intensity and duration of the homeopathic consultations may thus be advantageous for the treatment (7).

#### **9.4.2 Risk profile for homeopathic remedies**

Homeopathic remedies are mostly considered harmless in terms of safety concerns. However, some aspects of the production of homeopathic medicines might constitute potential safety

hazards. Firstly, not all homeopathic medicines administered are of high dilutions and remedies in low dilutions may cause harm if administered too frequently over a long period of time. If a homeopathic remedy made from a mother tincture is administered in its most concentrated form, it may cause direct harm if the patient is sensitive to the source material (6). Secondly, homeopathic medicines are produced from a wide range of natural or synthetic sources such as minerals and chemicals, as well as plant materials, including roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae; microorganisms, including fungi, bacteria, viruses and plant parasites; animal organs, tissues, secretions, and cell lines. Human materials may include tissues, secretions, hormones, and cell lines. Some of these source materials constitute potential safety hazards, since all materials of animal or human origin may contain pathogenic agents (6). Thus, it is vital to ensure high quality on the source materials and the excipients applied in the manufacture of homeopathic medicines to avoid risky situations. Failure of good manufacturing practice may result in major quality and safety concerns such as misidentification, impurity of starting material, cross-contamination or incidental contamination (6).

In the European Union homeopathic medicines are legally termed *homeopathic medicinal products*, and consist of medicines with a botanical, chemical, mineral or zoological origin (54). Homeopathic medicinal products are subject to the same requirements as other medicinal products regarding manufacturing procedures, technical quality, and all other requirements with the possible exception of documentation of efficacy (52). Thus, registration or marketing authorization for homeopathic medicinal products is always granted at the national level. In Norway homeopathic medicines are classified as medicinal products. Normally all medicines require separate marketing permissions from the Norwegian Medicines Agency. However, homeopathic medicines are exempted from these requirements and may be sold as long as the country of production (inside the EU) has granted permission for marketing (53). Most homeopathic medicines can be bought without prescriptions. The directive 2001/83/EC of the European Parliament and of the Council of 6 November, 2001 on the Community code relating to medicinal products for human use states that “no medicinal product may be placed on the market of a member state unless a marketing authorization has been issued by the competent authorities of that member state in accordance with this delivery or an authorization has been granted in accordance with Regulation (EEC) No 2309/93” (53).

Adverse effects of homeopathic remedies have been investigated by Dantas and Rampes (54). They stated that there was a rate of 9% for adverse effects in patients using homeopathic remedies in contrast to 6% in the placebo group. A meta-analysis (55) of 3,437 patients in 25 placebo-controlled RCTs, reported 33 cases of adverse effects for patients treated with homeopathy and 97 for patients treated with placebo. Data from observational studies and surveys (38) reveal that reported adverse effects from homeopathic treatment fluctuates between 2% (5) and 11% (56). Cases of adverse effects related to homeopathic practice have been reported in the literature (3, 57, 58), and a systematic review of case reports published in 2012 (64)(59) found that among the 38 primary reports included, 30 pertained to direct adverse effects of homeopathic remedies and another eight were related to adverse effects caused by substituting homeopathy for conventional medicine.

In conclusion, direct risk in homeopathy is found to be low. However, remedies of low dilutions are connected with direct risk associated with the pharmacologically active remedy. In addition, these remedies may impose indirect risk that is linked to practice and the concept of homeopathic aggravation (figure 9-4). As previously discussed, remedies of high dilutions cannot have a pharmacological effect and a direct toxicological risk from these remedies is impossible. The risk related to the remedies of high dilutions is therefore indirect and related to homeopathic practice (see figure 9-4). With regard to homeopathic theory and potential risk to patient safety the concept of homeopathic aggravation may represent the greatest threat since it allows an increase of symptoms as a part of a healing process.

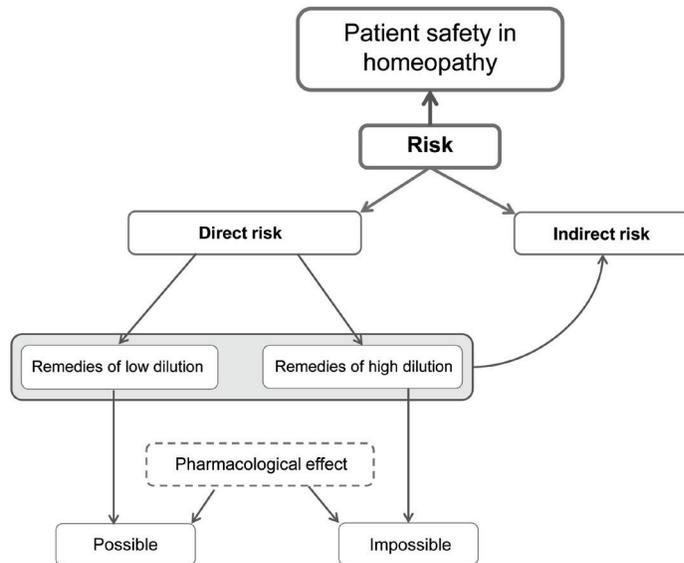


Figure 9-4 Risk in homeopathy with regard to possible pharmacological effects. Direct risk is only possible for homeopathic remedies of low dilutions. However, remedies of low dilutions may also impose indirect risk due to homeopathic practice. Adverse effects related to remedies of high dilutions must be due to indirect risk factors.

### Homeopathic aggravation

According to homeopathic philosophy, homeopathic aggravation is a “temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription”. In homeopathic theory, homeopathic aggravation is generally seen as a favorable response to treatment and is expected to be followed by an improvement (7, 48, 60). George Vithoulkas (a respected homeopathic practitioner and author in the homeopathic community) defined initial aggravation even as the optimal reaction to be expected from correct, constitutional remedy (61). Therefore, in homeopathic theory, a temporary deterioration of the patient’s health status as part of the therapeutic process is widely accepted.

The literature available regarding the occurrence of homeopathic aggravation in clinical practice, remains unclear. Some authors estimate that 75% of all chronic cases demonstrate appreciable aggravation of their symptoms during homeopathic treatment (60, 62). Other authors report a lower frequency of 10-20% in clinical practice (55). In a systematic review of homeopathic aggravations, Grabia and Ernst found, that four included trials reported 40 cases of aggravation in the placebo groups and 63 cases in the homeopathy groups. The authors concluded that although the included RCTs mentioned the phenomenon of homeopathic aggravations, the evidence was not strong

enough to provide support for the existence of aggravations. In conclusion, even though the physiological and pathophysiological basis of homeopathic aggravation remains unclear, the described worsening of symptoms and deterioration of the patients' health status during homeopathic intervention appears to be frequent and thus relevant with regard to patient safety.

### 9.4.3 How to differentiate between adverse effects and homeopathic aggravations

According to conventional medicine, the worsening of the patients' symptoms as a consequence of treatment is understood as adverse effect. Consequently, homeopathic aggravation is a part of the category adverse effects in conventional medicine. However, according to homeopathic theory, homeopathic aggravation is an independent concept from adverse effect and worsening of the symptoms is accepted to a certain degree and monitored as a part of the healing process. The figure below illustrates the different concepts.

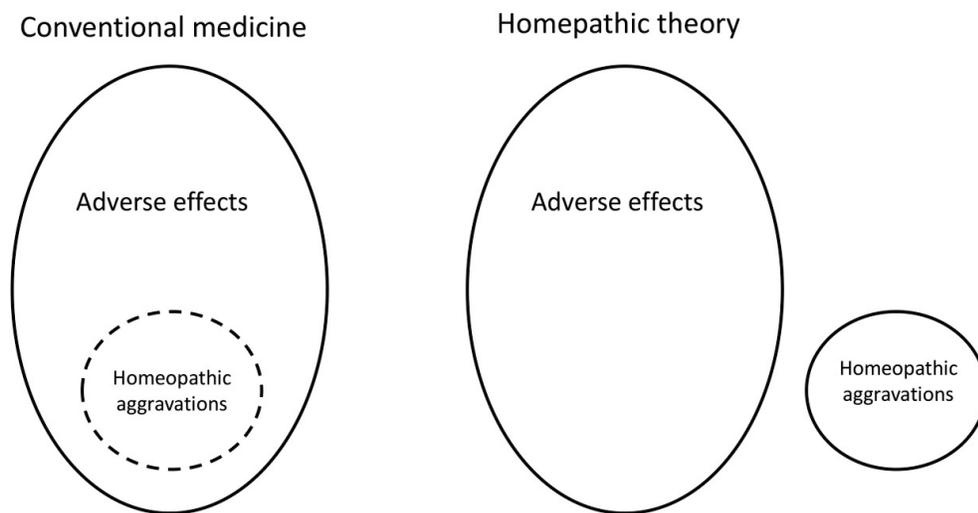


Figure 9-5 Based on conventional medical theory, homeopathic aggravation is defined as adverse effect. However, according to homeopathic theory the concept is distinct from adverse effect.

Since homeopathic aggravation, according to homeopathic theory, is tolerant towards worsening of the patients' symptoms, it is important that the homeopaths increase their awareness of adverse effects. It is important with regard to patient safety, that homeopaths do not ignore signs of serious adverse effects and thus provoke a dangerous situation for the patients. Consequences of overlooking serious symptoms are demonstrated in the case presented previously in this dissertation (3) and in a systematic review recently published (59).

There are several reasons for the need of criteria, acceptable to homeopaths that distinguish between acceptable homeopathic aggravations and adverse effects that make conventional treatment mandatory. Firstly, and most relevant, it will enhance patient safety, and secondly, it will allow comparison of safety data across studies which have to date no uniform definition of adverse effect vs. homeopathic aggravation. According to Hahnemann (the founder of homeopathy) (63) homeopathic aggravation consists of the same symptoms as the natural disease, whereas Kent (respected author and homeopath), argues that the symptoms of aggravation may be new symptoms that are different from those initially presented by the patients (64). Therefore, there was a need for developing a clear definition of homeopathic aggravation as compared to adverse effect that could serve as a basis for this research plan (65, 66).

### **9.5 Aims of the research plan**

Previous research suggests that there is low direct risk related to homeopathic remedies. However, homeopathic aggravation which is a concept unique to homeopathic practice, may impose indirect risk since it is tolerant towards a worsening of the patients' symptoms. Therefore, the global aim of this research plan was to explore, and provide more knowledge about patient safety in homeopathy, with a specific focus on risk related to the concept of homeopathic aggravation. Furthermore, initiate the development of a reporting system for adverse effects in homeopathy in order to enhance patient safety. The table at the next page presents the overarching aims (the specific aims will be reported along every single study separately), research questions and methodology applied in this research plan.

Table 9-2 The aims, research questions and methodology applied in this research plan.

<b>Aims</b>	<b>Research questions</b>	<b>Methodology</b>	<b>Publication</b>
<ul style="list-style-type: none"> <li>To estimate whether homeopathic treatment is associated with risk.</li> </ul>	<ul style="list-style-type: none"> <li>Status of problem reported in the scientific literature.</li> <li>Initiate the development of a reporting system for adverse effect.</li> </ul>	<ul style="list-style-type: none"> <li>Systematic review and meta-analysis. Application of the CTCAE grading system by the first author, grading of adverse effects and homeopathic aggravations.</li> </ul>	1
<ul style="list-style-type: none"> <li>To explore and define the concept of homeopathic aggravation as specificity of homeopathic theory.</li> </ul>	<ul style="list-style-type: none"> <li>Definition of the concept of homeopathic aggravation.</li> <li>Development of criteria, which discriminate the concept of homeopathic aggravations from adverse effects.</li> <li>Assess patient safety.</li> </ul>	<ul style="list-style-type: none"> <li>Focus group interview among lay homeopaths.</li> <li>Focus group interview among medical homeopaths.</li> </ul>	2, 3
<ul style="list-style-type: none"> <li>To evaluate whether the concept of homeopathic aggravation imposes a particular risk on the patient.</li> </ul>	<ul style="list-style-type: none"> <li>How common are adverse effects in homeopathic practice?</li> <li>Severity of adverse effects in homeopathic practice according to the CTCAE grading system.</li> <li>Application of criteria to discriminate between homeopathic aggravation and adverse effects.</li> <li>Comparison of adverse effects and identified homeopathic aggravations with regard to the CTCAE criteria.</li> </ul>	<ul style="list-style-type: none"> <li>Survey among homeopaths.</li> <li>Applying the ICPC-2 coding for classification of initial complaints reported by patients.</li> <li>Identification of adverse effects.</li> <li>Application of the CTCAE grading system by two MDs independently, grading of adverse effects.</li> <li>Differentiating homeopathic aggravations from adverse effects by applying the newly developed criteria. The process was performed by two homeopaths independently.</li> <li>Comparing the identified homeopathic aggravations with the remaining adverse effects with regard to their severity (CTCAE grading system).</li> </ul>	4

## **10 Methods and results for this research plan**

In this section each individual study will be presented separately, including the following paragraphs.

1. Specific aims of the study
2. Specific methodology applied in the study
3. Abstract of the publication

The rationale for this strategy was that each individual study has different, yet interdependent methodologies.

### **10.1 General methodology applied in this research plan**

Mixed method research is a recognized study design where the researcher mixes or combines quantitative and qualitative research techniques, methods, approaches, concepts or language within one research plan (67, 68). It allows the researcher to select and match design components that offer the best prerequisite to answer the research questions, and the design is a complement to traditional qualitative and quantitative research (67, 68). Quantitative research is often used to measure outcome from an intervention and support to generalize results from a qualitative study. In this research plan, quantitative research was applied to estimate risk and to evaluate how frequent adverse effects was reported in homeopathic practice. Qualitative research can generate hypotheses for quantitative research and test the theoretical framework for a quantitative method (69). The qualitative approach can help the researcher to gain access to the view of participants and can address how an intervention is used in practice (68, 69). In the present research plan, qualitative research was applied to develop a definition of concepts and criteria unique for homeopathic practice based on the views of the homeopaths. Both research approaches can provide information about different aspects of a phenomenon, which was the intention for applying the research design in this research plan.

### **10.2 Paper I: Adverse effects of homeopathy, what do we know? A systematic review and meta-analysis of Randomized Controlled trials**

#### **10.2.1 Aims**

The specific aims were:

1. Systematically investigate how homeopathic aggravations and adverse effects are reported in randomized controlled trials.
2. Classify adverse effects and homeopathic aggravations according to the Common Terminology Criteria for Adverse Events (CTCAE).
3. Perform a meta-analysis in order to evaluate the risk for patients using homeopathy (consultation and/or homeopathic remedies) compared to the controls.

## **10.2.2 Method**

### **10.2.2.1 *Systematic review and meta-analysis***

The purpose of a systematic review is to provide clinicians, nurses, therapists, healthcare managers, policy makers and consumers with quality information on the effectiveness, safety, meaningfulness, feasibility and appropriateness of a large number of healthcare interventions. This method is appropriate when the researcher wants to investigate safety issues related to homeopathy.

A systematic review is considered to provide the highest level of evidence in regard to the effectiveness of the interventions for a specific condition (70). In order to answer a specific research question, a systematic review has the potential to collect all empirical evidence included in the eligibility criteria (71) and minimize bias to provide reliable findings.

Meta-analysis is a statistical combination of results from two or more separate studies (71). The potential advantages of meta-analyses include increase in power, an improvement in precision, and the ability to answer questions not posed by individual studies. Meta-analyses have however, the potential to adversely mislead the results, particularly in cases of a) inaccurate consideration of inappropriate study designs, b) biases within the studies, c) variation across studies, and d) reporting biases.

### **10.2.2.2 *Common Terminology Criteria for Adverse Events (CTCAE)***

The CTCAE guidelines include a descriptive terminology which can be utilized for reporting adverse events (36). The general CTCAE guidelines cover grades 1-5 where 1 is mild, 2 moderate, 3 severe or medically significant, 4 is life threatening and 5 lethal.

### **10.2.3 Abstract paper I**

#### **Background**

Despite unclear mechanisms of effect and safety, homeopathic remedies are in widespread use. To enhance patient safety, it is, therefore, essential to investigate risk associated with this treatment modality, particularly since adverse effects after homeopathy have been reported. A particularly important concept, which is unique to homeopathy, is homeopathic aggravation that reflects a transient worsening of the patients' symptoms, before an expected improvement occurs. Moreover, it is vital that a distinction between homeopathic aggravation and adverse effects is established. There is a lack of systematic information on how frequent adverse effects and homeopathic aggravations are registered in studies. Therefore, a systematic review and meta-analysis were performed.

#### **Method/Findings**

Sixteen electronic databases were searched for Randomized Controlled Trials with data regarding adverse effect and/or homeopathic aggravations. The searches were limited from the year 1995 to January 2011. Forty-one RCTs, with a total of 3967 participants were included. A subtotal of 35 studies was included in the additional meta-analysis.

#### **Results**

A total of 68% of the included trials reported 806 adverse effects after treatment, and 12% reported 108 homeopathic aggravations. Both were classified mainly as minor (grade 1) and moderate (grade 2) according to the Common Terminology Criteria for Adverse Events, apart from five cases of homeopathic aggravations that were classified as serious (grade 3). The meta-analysis found that adverse effects were reported to a similar degree in the placebo/ active control groups than in the homeopathy groups. The methodological quality was high, according to a method recommended in the Cochrane handbook for RCTs, was high.

#### **Conclusion**

Adverse effects and homeopathic aggravations were mainly reported as mild to moderate according to the CTCAE grading system. However, some cases of serious adverse effects were reported, which highlights the need for criteria that distinguish adverse effects from homeopathic aggravations. These results suggest a similar risk for homeopathic treatment compared to placebo and active controls, such as conventional medicine. The inconsistent use of safety terminology in the included studies was problematic and may bias this result.

### **10.3 Paper II: Is it possible to Distinguish Homeopathic Aggravation from Adverse Effect? A Qualitative study**

#### **Paper III: The Red Flag! Risk assessment among medical homeopaths in Norway: A qualitative study**

The method and aims for these two individual studies were more and less similar. They will therefore be presented in the same section. The types of study participants, however, differed. In study II the participants were lay-homeopaths and in study III they were medical homeopaths.

#### **10.3.1 Aims**

The specific aim for study II was

1. To explore and compose criteria that may differentiate adverse effects from homeopathic aggravations.

The specific aims for study III were

2. How do medical homeopaths understand and discriminate between homeopathic aggravations and adverse effects in clinical practice?
3. How do medical homeopaths assess patient safety in their medical practice?

#### **10.3.2 Method**

##### **10.3.2.1 *Focus group interviews***

Qualitative methodology has been identified as fundamental to understand and describe the philosophical basis, key treatment components and contextual frameworks of CAM modalities (16, 72) in the field of CAM. This type of design is usually appropriate when existing theory or research literature on a phenomenon is limited (73). Focus group interview is a qualitative approach utilized to obtain in-depth knowledge and viewpoints from participants. In focus group interviews the study participants can discuss issues within the context of their own shared cultural background (74). The group interaction can generate unique insights into shared experiences and social norms, and is appropriate when the goal is to understand differences in perspectives between groups of people, or to uncover factors that influence opinions or behavior. This can be productive especially with socially marginalized populations, and in discussing potentially sensitive topics (75, 76). Furthermore, they may contribute to a deeper understanding and thorough knowledge of important health issues, especially in situations with limited knowledge of the phenomenon of interest (77). This type of interview is a method of explicit inclusion, which uses

the group interaction to generate data (78). The communication between the participating homeopaths provided new insight into the concepts that are unique for homeopathy. The dialogue between participants, which can reveal diversity regarding the understanding of adverse effects and homeopathic aggravations, was the decisive factor for utilizing focus groups, rather than individual interviews for this. The study participants had thorough experience operating as homeopaths from clinical practice, where they evaluated adverse effects and homeopathic aggravations on a daily basis. They were therefore able to debate the research questions as experts based on long-lasting experience as homeopaths.

#### **10.3.2.2 Homeopathic case analysis**

Case analysis explains how homeopaths evaluate patients. In such an analysis the homeopaths evaluate the patients' ability to recover, the extent of their illness and their plausible response to the treatment (7). The main goal is to determine the patients' general condition and the development of the disease. The homeopath will for example monitor the state of the entire organism, expressed in homeopathic theory as "energy level", "the mental-emotional state", and the "key symptoms" of the patient (79). If correctly applied, case analysis provides a "close-method" monitoring tool within homeopathic theory, which should allow identification of serious complications.

#### **10.3.3 Abstract paper II**

##### **Background**

Homeopathic aggravation is a temporary worsening of existing symptoms following the administration of a correct homeopathic prescription. The aim of this study was to explore and compose criteria for the purpose of differentiating homeopathic aggravation from adverse effect.

##### **Material and Methods**

A qualitative approach was employed using focus group interviews. Two interviews including a total of eleven experienced homeopaths were performed in Oslo in Norway. The practitioners had practiced classical homeopathy over a period of 10-32 years. For the analysis of text data a qualitative content analysis was applied. The definition of codes was composed prior to as well as during the data analysis.

##### **Results**

Aggravations were found to be subtle and multifaceted events. Moreover, there is a need for highly skilled homeopaths to identify and report aggravations. The definition of adverse effect

may be “an undesirable effect of a remedy”. This is a pragmatic and flexible definition, more in line with the holistic paradigm represented by the homeopaths. In addition, eight criteria distinguishing aggravation from adverse effect were composed. Highly sensitive persons hold a unique position regarding safety. Identifying these patients is imperative, enabling correct treatment and avoidance of undesirable treatment effects.

### **Conclusion**

This study comprised a rigorous exploration of the homeopaths’ views and experiences regarding aggravations and adverse effects. The eight criteria developed in this study may ensure patient safety and support therapists in their identification of “an undesirable effect of a remedy”.

### **10.3.4 Abstract paper III**

#### **Background**

Homeopathy is widely used, and many European physicians practice homeopathy in addition to conventional medicine. Adverse effects in homeopathy are not expected by homeopaths due to the negligible quantities of active substances in a remedy. However, the question was posed whether homeopathic aggravation, which is described as a temporary worsening of existing symptoms following a correct homeopathic remedy, should be regarded as adverse effects or ruled out as desirable events of the treatment. In order to improve knowledge in an unexplored area of patient safety, investigation was performed into how medical homeopaths discriminate between homeopathic aggravations and adverse effects, and how they assess patient safety in medical practice.

#### **Method**

A qualitative approach was employed using focus group interviews. Two interviews including a total of seven medical homeopaths were performed in Oslo in Norway. The participants practiced homeopathy as well as conventional medicine. A qualitative content analysis was applied to analyze the text data. The definition of codes was composed prior to as well as during the data analysis.

#### **Results**

According to the medical homeopaths, a feeling of well-being may be a criterion to distinguish homeopathic aggravations from adverse effects. There was disagreement among the participants regarding possible adverse effects as a result of homeopathic treatment. However, they agreed that when an incorrect remedy was administered, it could create a disruption or suppressive

reaction in the patients. This was not perceived as adverse effects but a possibility to prescribe a new remedy on the emergence of new symptoms. This study revealed several advantages for the patients as the medical homeopaths looked for dangerous symptoms, which may enhance safety. Moreover, the patients were given time and space, enabling the practitioners to see the complete picture. A more comprehensive toolkit provided the medical homeopaths with a sense of professionalism.

### **Conclusion**

This explorative qualitative study investigated the understanding and assessment of risk according to medical homeopaths based on their experiences from clinical practice. A feeling of well-being emerging shortly after having taken the remedy was the most important criterion for discriminating between homeopathic aggravations and adverse effects in clinical practice. The medical homeopaths applied the view of both professions and always looked for red flag situations in the consultation room. The combination of their knowledge from the two treatment systems may benefit the patients. These tentative results deserve further research efforts to improve the safety for patients using homeopathy. It is recommended that further research improve and develop concepts unique to homeopathy, thus, enabling validation and modernization of this medical practice.

## **10.4 Paper IV: Risk in homeopathy: Classification of adverse effects and homeopathic aggravations – A cross Sectional study among Norwegian Homeopaths**

### **10.4.1 Aims**

The specific aims were

1. To describe what kind of reactions, reported by the patients, two weeks after taking homeopathic remedies and to classify these into *no reactions*, *improvement of symptoms* and *worsening of symptoms*.
2. To grade the severity of the *worsening of symptoms* according to the Common Terminology Criteria for Adverse Events (CTCAE).
3. To classify the *worsening of symptoms* into homeopathic aggravations or adverse effects.
4. To describe the recommendations the homeopaths gave to their patients with regarding ongoing conventional medical treatment.

## **10.4.2 Method**

### **10.4.2.1 A cross-sectional study**

A cross-sectional study is often used to estimate the prevalence of a condition in a population and is often applied when calculating risk factors related to a disease (80). All information in a cross-sectional study is collected at a set point in time and provides a snapshot of the current situation, known as ‘point prevalence’ (81), which allows the researcher to obtain useful developmental data in a relatively short period of time. The design is intuitively easy to understand, and enables examination of many variables simultaneously (81).

### **10.4.2.2 International Classification of Primary Care (ICPC-2)**

The initial complaints reported by the study participants were classified according to the International Classification of Primary Care – 2nd edition (ICPC) (82). The system includes three important elements: i) Reasons for encounter (RFE), ii) diagnoses or problems, and iii) process of care. RFE reflect the patient’s view. Process of care (decision, action, intervention or plans) reflects the care process, and the assessment (diagnosis or health issue) reflects the physician’s view (82). It was a conscious choice to apply this classification system in the present study, as the ICPC-2 is a standard classification system and used worldwide. A standardized and validated system facilitates the comparison across studies.

## **10.4.3 Abstract paper IV**

### **Introduction**

Patient safety is central for all health care practices and registration of adverse effects is done to identify treatment that might pose a risk for patients. In homeopathy there is an ongoing discussion of how to classify a reaction to treatment as adverse effect (AE) or homeopathic aggravation (HA). Homeopathic aggravation is understood as a temporary worsening of existing symptoms following the administration of a homeopathic remedy, which is subsequently followed by an improvement. However, this concept may impose a particular risk, as it is tolerant towards a worsening of the patients’ symptoms. The aim of this study was therefore to explore classification of patient reported reactions as AE or HA.

### **Methods**

In a cross sectional survey, patients were asked to register any reactions they had experienced 14 days after an initial homeopathic consultation. Two Medical Doctors (MDs) evaluated all reported worsening of symptoms and graded these for severity according to the Common

Terminology Criteria for Adverse Events. Then two homeopaths evaluated and classified the symptoms as homeopathic aggravations according to whether it was i) increase of patient's existing symptoms, ii) and/or a feeling of well-being that emerges 1-3 days after taking the remedy, iii) and/or headache and/or fatigue may accompany these symptoms.

## **Results**

Among the 288 participants, 154 (53%) reported no reactions, 60 (21%) improvement and 74 (26%) worsening of symptoms (adverse effects). The adverse effects was classified as CTCAE grade 1 (minor, 66%) or 2 (moderate, 34%), while none were graded as grade 3 (serious), 4 (life-threatening), or 5 (lethal). A total of 49 (66%) participants experienced adverse effects that were classified as homeopathic aggravations (HA, 17% of all participants). Of these 73% (n=36) were classified as CTCAE grade 1 and 27% (n=13) as grade 2. For those that were classified as adverse effects (9% of all participants), 52% (n=13) was grade 1 and 48% (n=12) grade 2, giving a tendency towards milder severity for those classified as HA (p=0.065).

## **Conclusion**

Patients reported a substantial part of the short-term reactions after taking homeopathic remedy (medication) as a worsening of symptoms. These reactions were classified only as mild or moderate adverse effects. There was a tendency for homeopathic aggravations to be classified as less severe. More studies are needed to confirm the existence of homeopathic aggravation and, accordingly, how to classify the concept in a clinical meaningful way.

## **11 Discussion**

Findings from this research suggest that homeopathy is generally associated with low direct risk, which is in line with international studies. Moreover, direct risk is only possible for homeopathic remedies of low dilutions since they have possible pharmacological effects. However, remedies of low dilutions may also impose indirect risk due to homeopathic practice. Remedies of high dilutions cannot have a pharmacological effect and a direct toxicological risk from these remedies is impossible. The risk related to the remedies of high dilutions is therefore indirect and related to homeopathic practice

The concept of homeopathic aggravation imposes a particular risk, as it allows the health status of the patient to deteriorate before it improves. Therefore, the practitioner in clinical practice must decide whether the deteriorations of the patient's symptoms are homeopathic aggravations or not. In the guidelines developed to distinguish homeopathic aggravation from adverse effect in this present research plan, it turned out that a feeling of well-being was the most important criterion (papers II and III). From a safety perspective, however, the time based criterion (1-3 days) may ensure that patients are referred to conventional care in due time. Consequently, there will be a probable increase in the number of patients being referred to conventional care. A time-based criterion allows differentiating the concept homeopathic aggravation from adverse effect within homeopathic theory, and thus has a good potential for acceptance among homeopaths. In addition, clear definitions and criteria are important and will moreover improve the internal validity of the study.

It is furthermore important to compare data on homeopathic aggravations from multiple studies in a reporting system. A reporting system for adverse effects should provide the following information:

1. Differentiate adverse effects from homeopathic aggravations
2. Patients included in research should have their symptom patterns rated at baseline before the intervention begins
- 3 Adverse effects should be reported separately for treatment and control groups.
4. If possible, the exact number of adverse effects should be reported in all subjects
5. A grading system, such as the CTCAE, should be used when reporting adverse effects and homeopathic aggravations.

### **11.1 How frequent are adverse effects with regard to homeopathic treatment?**

According to the findings from this research plan, there is clear evidence for the appearance of adverse effect related to homeopathic treatment. When applying the definition of homeopathic aggravation, a total of 9% of the study participants reported adverse effects. The adverse effects were graded as CTCAE grades 1 or 2, understood as mild to moderate events (papers I and IV).

Results from other studies demonstrate that adverse effects related to the homeopathic remedy fluctuate between 2% (5) and 11% (56). However, the magnitude and seriousness of risk related to conventional medications are evidently higher. In a systematic review of the use of Aspirin (acetyl-salicylic acid), involving 9 studies and more than 1,000 participants, a 30% increase in the risk of serious bleeding was demonstrated (83).

Remedies of low dilution that are made from mother tinctures are principally able to be pharmacologically active. These remedies may be administered in concentrated forms (D6 or D12) and have a risk profile similar to that of herbal medicine (6). Some homeopathic remedies are produced from sources constituting potential risk hazards (6), such as remedies that are made from animal and human sources, which may contain pathogenic agents that represent a risk of contamination. Hence, satisfactory manufacture practice is imperative to avoid safety hazards.

Almost half of the lay homeopaths included in this research plan (65), claimed that homeopathic treatment in general does not cause any adverse effects, which clearly does not represent published research or clinical practice (54, 59). Therefore, it is important to increase the awareness of potential adverse effects among homeopathic practitioners. In order to enhance safety, the homeopaths should make sure that their patients receive a conventional diagnosis for their complaints or diseases if the worsening of symptoms lasts for more than three days. However, this is not applicable for all complaints for example high fever in children. The case study presented in the introduction (3) demonstrates how serious the consequences of homeopathic treatment can be. Furthermore, it highlights the need for an appropriate and relevant training for homeopaths, and a reporting system for adverse effects. Moreover, it reveals the need for criteria that enable homeopaths to distinguish between adverse effects and homeopathic aggravations, and which gives a clear signal, when the condition of the patient is beyond their skills.

In conventional medicine, adverse effects of the treatment are accepted to a certain degree. The reason is that the beneficial effects of the treatment will compensate for them. For example, in cancer treatment, chemotherapy is related to severe adverse effects, such as nausea, fatigue and heart failure. This is accepted since the beneficial effects of the treatment are to shrink the tumor and, thereby, fight the cancer. Hence, the advantages exceed the disadvantages. This is especially true for patients with severe diagnoses, who are more willingly to endure severe adverse effects, as long as they are eventually healed. For patients with less severe diagnoses, adverse effects are

unacceptable. However, in homeopathy, patients with for example atopic eczema are willing to endure deteriorations they otherwise would have rejected, because they anticipate a subsequent improvement. Consequently, this implies risk for the patient, and it is imperative that the homeopaths evaluate the symptoms properly, and refer the patient to conventional care when necessary.

Findings from this research demonstrated frequent incidences of adverse effects in homeopathic practice, including those interpreted as homeopathic aggravations. It was found that two out of three adverse effects reported by patients after taking a homeopathic remedy can be classified as homeopathic aggravation. More importantly, there was no difference in severity between homeopathic aggravations and adverse effects, suggesting similar risk profiles between the two concepts. Even though there was a trend for homeopathic aggravation to be classified less severe. Compared to other studies, the frequency of homeopathic aggravations was found to be higher (17%) in the studies presented here. In other studies the frequency of homeopathic aggravations fluctuated between 6% (64) and 8% (5).

Homeopathic aggravation may induce a particular risk to patients in homeopathy, because the patients may suffer from deteriorations in their health status. This may further complicate the patients' treatment, or excessively delay the consultation with their GP. It is therefore important that the homeopaths in clinical practice, closely observe and monitor the patients' symptoms in order to decide the direction of the therapeutic process, for instance towards a further deterioration or improvement of the symptoms (7, 79). Results from the present research suggest that homeopaths applied homeopathic case analyses when evaluating the patients' symptoms in order to avoid hazardous situations (7). However, if the homeopaths do not possess the knowledge required the concept of homeopathic aggravation may impose risk for the patients. Moreover, it is important to determine the patients' symptoms as homeopathic aggravations or adverse effects. Findings from this research suggest that both lay as well as medical homeopaths are able to make this distinction accordingly (65, 66). Moreover, the patients would benefit from improved cooperation between lay homeopaths and medical doctors, because this desirable situation will enhance patient safety. Furthermore, patients highly valued input from their medical doctors about the use of CAM (84). A study by Breitsameter (85) however, identified ethical problems

regarding the physicians' inability to provide information about the combination of CAM, including homeopathy, and conventional care.

A pragmatic and descriptive definition of homeopathic aggravation was utilized in this study, without suggesting any physiological and pathophysiological mechanisms for the concept. The operative definition allowed the identification of situations within homeopathic theory, where conventional care is unequivocally needed. This approach will increase patient safety within homeopathic practice.

### 11.2 Is homeopathy generally safe?

In conclusion, homeopathic treatment is generally associated with low direct risk (5, 38, 54, 86) and the data from the research presented here confirm these results. The risk profile of the homeopathic remedies is minor, however, there is a potential for indirect risk related to homeopathic practice (see figure 11-1). In that respect it is imperative to distinguish homeopathic aggravations from adverse effects as homeopathic aggravation may impose a particular risk on patients. The criteria developed may assist homeopaths in distinguishing between homeopathic aggravation and adverse effects. Furthermore, the results show that adverse effects and homeopathic aggravations are common in clinical practice. However, the events were classified as mild to moderate with no difference between homeopathic aggravations and adverse effect with regard to severity.

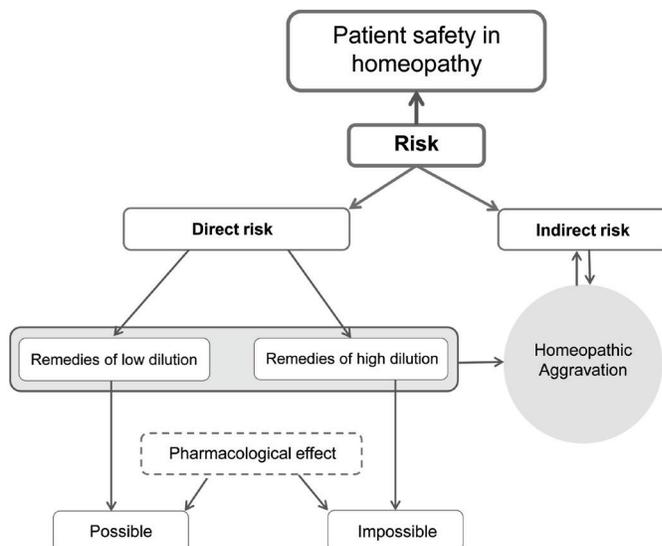


Figure 11-1 Pharmacological model in association with indirect risk in homeopathy. Indirect risk is related to clinical practice, the practitioner and applies likewise to remedies of low and high dilutions. In clinical practice the practitioner must decide whether the deteriorations of the patient's symptoms are homeopathic aggravations or not. The developed criteria to distinguish between homeopathic aggravations and adverse effects will provide a tool within homeopathic theory to facilitate this process.

### **11.3 The concept of homeopathic aggravation: Potential explanations unrelated to homeopathic theory and a general risk evaluation**

#### **11.3.1 Nocebo effect**

Homeopathic remedies may impose risk known as the nocebo effect (21). Nocebo effects are defined as the development of negative effects that are attributed to a medication, albeit the drug itself does not cause the provocation of these symptoms (21, 87). The development of adverse effects after placebo intake has been reported for medical conditions such as depression (88) and cancer (89). Nocebo effects are estimated to account for 72% of drop-outs in drug groups of fibromyalgia trials (90). Observations from clinical trials indicate that patients' expectations play an important role in the development of nocebo effects. If patients were informed about potential adverse effects of a specific drug, they reported more symptoms than patients who were given limited information about potential adverse effects (91). Moreover, it seems that conditioning (Pavlov's dogs) and associative learning may activate the development of nocebo effects, although there is weaker evidence for their involvement in nocebo effects compared to their role in developing placebo responses. A frequently cited clinical example for the conditioning of adverse effects is the development of anticipation nausea in patients undergoing chemotherapy (21).

Data from this research (paper IV) demonstrated that patients rather often experienced homeopathic aggravations during treatment. An explanation for such a high frequency may be that many homeopaths inform their patients that homeopathic aggravations might occur during treatment. Health care providers should be aware that all interactions with the patients have the potential to result in expectations. Consequently, information that patients receive prior to treatment is of particular relevance (21).

#### **11.3.2 Natural history of disease**

The natural history of a disease is a theory about the diseases' normal course in the absence of an intervention. The central question for studies of prevention and treatments (clinical trials) is whether the use of a particular preventive or treatment measure can change the natural history of

the disease in a favorable direction, by reducing or preventing clinical manifestations, complications or death (41). The natural history of disease refers to a description of the uninterrupted progression of a disease in an individual from the moment of exposure to causal agents until recovery (figure 10-2). Knowledge of the natural history of disease is important for disease prevention and control. Moreover, the natural history of disease is one of the major elements of descriptive epidemiology (41) (see figure 10-2). Modification of the model has been made for study purposes.

If a patient visiting a homeopath experiences worsening of the symptoms, the homeopath must evaluate the situation. If the patient sees the homeopath during a point in time, when the symptoms are close to peak, he or she will experience an initial worsening of symptoms, followed by an improvement. Therefore, homeopathic aggravations may be understood as the “natural history of disease” as the patients will experience a worsening of the symptoms, even if they simultaneously experience a feeling of well-being (improved sleep). This is visualized in figure 11-2 through the escalating curve. If the worsening of these symptoms lasts for more than three days, and the patients feel worse, and there are no signs of well-being, it must be regarded as adverse effects, or the disease is more severe than anticipated (please see section 11.3.3 “The iceberg model”, also see fig 11-4). Consequently, the curve will peak at a much later stage. In these cases the homeopaths have to refer the patients to conventional care.

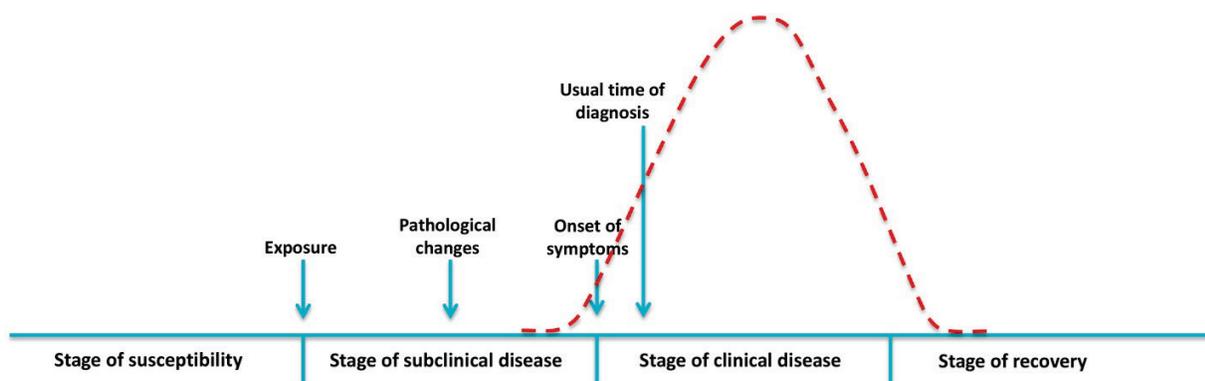


Figure 11-2 The natural history of disease.

Reference source: Centers for Disease Control and Prevention. Principles of epidemiology, 2nd ed. Atlanta: U.S. Department of Health and Human Services; 1992.

It can be assumed that a pathological condition, such as a knee pain, will peak at some point and then eventually subside as long as it does not follow a chronic course. An ineffective treatment

will not influence the natural course of the disease, whereas an effective treatment will lower the peak and most likely flatten the slope of the curve, so that the symptoms are either less intense and/or will subside earlier. This scenario is visualized in figure 11-3.

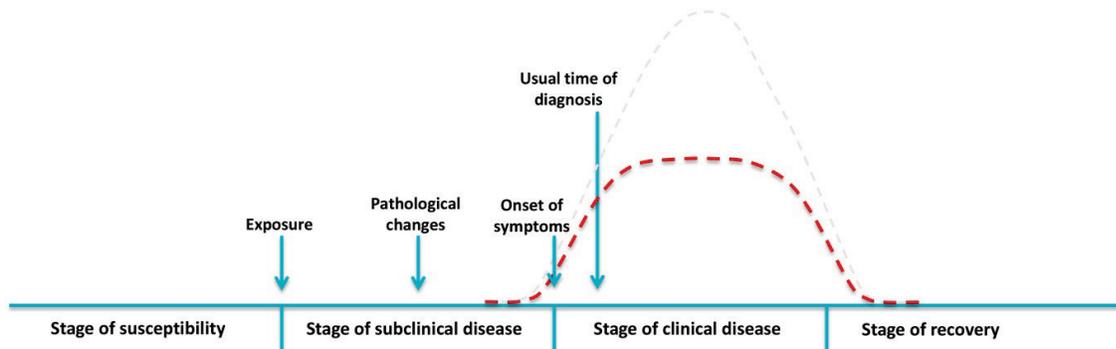


Figure 11-3 Improvement of symptoms which flattens the curve following an intervention.

Reference source: Hoffman GA, Harrington A, Fields HL. Pain and Placebo: What we have learned. *Perspectives in Biology and Medicine*. 2005; 48(2): 1708-12.

Research related to placebo suggests that patients will seek treatment when the symptoms are at their most intense, meaning near the peak of the curve. Hoffmann et al (92) postulate that as the patient's initial symptoms are at the worst when visiting a practitioner, the patient will most likely experience a decrease in the symptom level at the second visit to the practitioner. The decreased symptoms may be attributed to the treatment, placebo, to the natural history of the disease (41, 93).

If a patient with common cold symptoms suddenly deteriorates during the night, with a temperature increase beyond 40 degrees, and develops a rash that does not disappear when a drinking glass is pressed to the skin, and complains about pain in the neck, the situation is serious. This patient must be sent to the hospital immediately, as the possible presence of bacterial meningitis is strong. This scenario is visualized in figure 11-4 below.

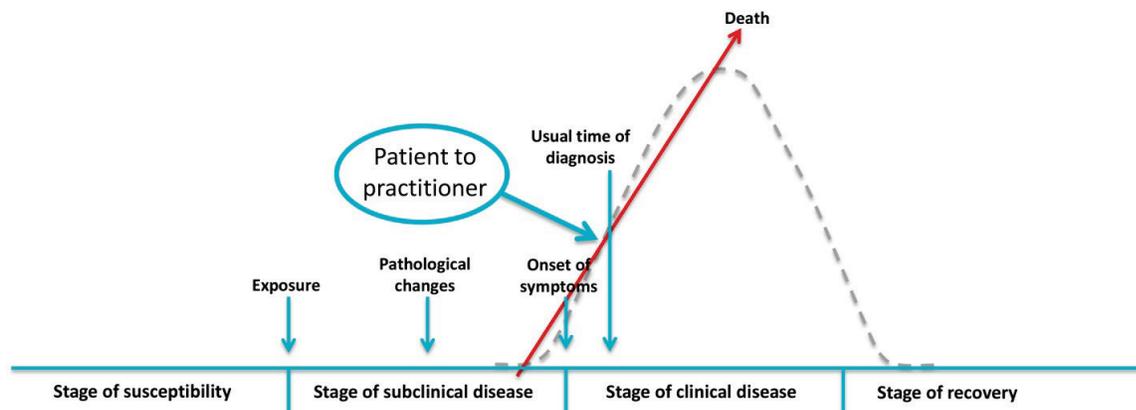


Figure 11-4 Acceleration of symptoms in an acute situation.

When assessing the symptoms of the patients, the homeopaths may apply the model as described in papers II and III. If the symptoms are severe, last for more than three days and there are no therapeutic signs, such as a feeling of well-being, the symptoms must be regarded as a severe adverse effect or a representation of much more severe and different diagnoses with an initially similar symptom pattern.

### 11.3.3 The iceberg model

Hemingway had a style of writing he referred to as *the iceberg theory* in which written words in a story focus on surface facts, those easily seen. However, beneath and behind the words is a more complete structure supporting the story. In the theory of diseases, *the iceberg model* is a metaphor emphasizing that for virtually every health problem, the number of known cases of disease is outweighed by those that remain undiscovered (94), much as the unseen part of an iceberg is much larger than the part that is visible above the water (95). In order to fit the purpose of the present research, the iceberg model has been modified and connected to the theory about the natural course of disease. In this way the model can be applied to individual health issues (see figure 11-5).

Catching a cold is normally an event that occurs once or twice during the winter season and many patients seek the help from a homeopath, especially if this is a recurring event. If the symptoms of a cold persist and the patient develops fatigue and weakness, the homeopath should be concerned and closely follow the patient on a daily basis. These symptoms are unacceptable and the patient should be referred to conventional care if no signs of improvement appear. If it turns out that the patient is then diagnosed with pneumonia, the cold was “the top of an iceberg”. The

cold represented superficial symptoms, while a far more serious disease that was developing underneath (figure 11-5). In order to ensure patient safety in such cases, it is important that the homeopath follows the patient carefully by assessing the symptoms frequently, and refers the patient to conventional care, if no therapeutic improvements appear.

Another, even more serious example is a patient with cough, shortness of breath and breast pain who visits a homeopath and is later diagnosed with lung carcinoma. Therefore, the iceberg model suggests that an awareness of potentially serious differential diagnoses is mandatory for a practicing homeopath, so the patient is transferred immediately to conventional care, if the first sign of a “red flag” situation occur. An awareness and alertness for red flag situations should always be present when observing and monitoring patients’ symptoms.

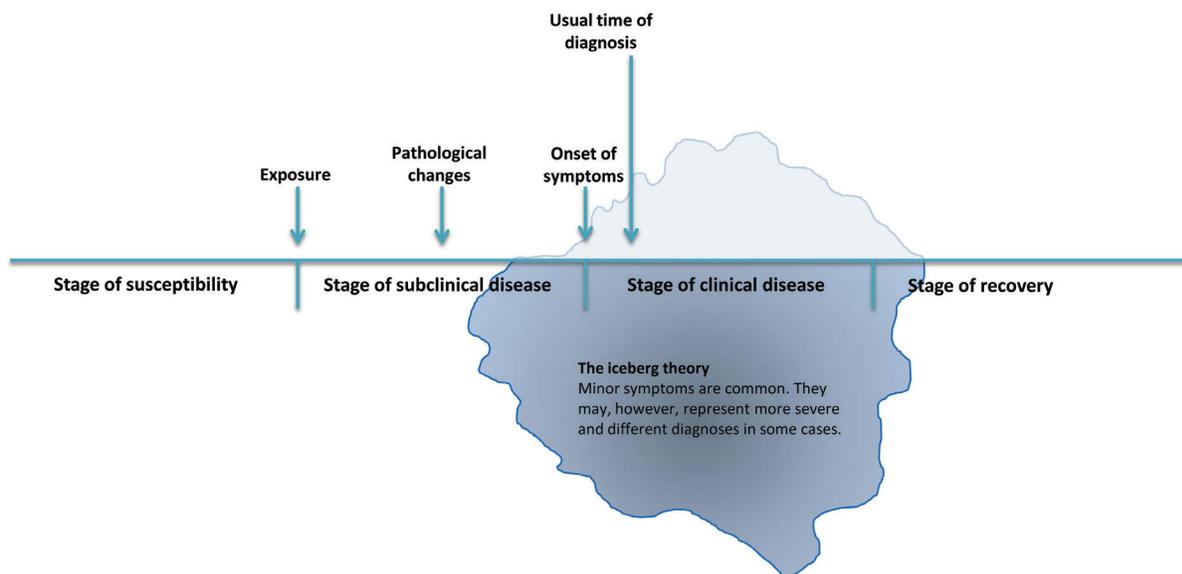


Figure 11-5 The iceberg model emphasizes that minor complaints or symptoms are common, but they may represent more severe different diagnoses.

## 11.4 Methodological aspects

### 11.4.1 Focus group interview

In this research plan a qualitative content analysis was applied to analyze the transcribed interviews. A content analysis is a systematic examination of text by identifying and grouping themes, classifying and developing categories and performing the coding (78). The analysis is a flexible method of analyzing text data (73).

Content analyses are usually applied when theory or prior research exist, but the research or theory are incomplete or would benefit from further investigation (73). This was the rationale for applying the analysis in the present research plan. Moreover, the success of content analyses depends on the coding process. In the two qualitative studies presented here, the codes were defined both prior to and during the data analysis. Hence, we used elements from conventional and direct content analyses (mixed type). The basic coding process was organized in large quantities of text, which was further adapted into fewer categories (96). Codes defined prior to the interviews were related to the main topics of the studies, such as homeopathic aggravations and adverse effects. The codes *the benefit of using both homeopathy and conventional medicine* (article III) and *highly sensitive patients* (article II) emerged from the data material. This coding enabled emergence of new aspects of the themes in question.

The coding and categories were also organized according to homeopathic case analyses (7). Case analyses explain how homeopaths evaluate their patients and explore the various steps in the treatment process. The homeopaths assess patient's symptoms, the patient's ability to heal, and how they respond to the treatment in this process. The application of this approach enhanced the reliability of the present study as it anchors the coding and categories to clinical practice.

The candidate has worked in clinical practice as a homeopath for nearly 30 years. This background was an advantage when selecting homeopaths for this study, as the candidate knew that highly skilled homeopaths were needed to get solid information about homeopathic aggravations. It takes several years of clinical practice to become experienced in evaluating the patients' symptoms and, thus, being able to add new aspects to the field. This selection criterion may, however, have biased the findings in this study, as the selected informants might have represented background and experience akin to those of the candidates, while other categories of homeopaths were excluded. We believe, however, that the selection of skilled and experienced homeopaths has provided reflections firmly rooted in the Norwegian homeopathic tradition.

The two co-authors of the qualitative papers are not homeopaths, nor do they have in-depth knowledge of homeopathic theory. However, one of them is a social scientist with previous research experience in risk communication and risk perception among CAM patients (97, 98), and the other has experience from clinical practice and research regarding adverse effects in acupuncture (99). Both of them have experience with qualitative research and have contributed to

reflections of the codes in the analyzing process. This can be viewed as a triangulation of the results. Such an analytic approach enhances the reliability of the study.

To reduce bias and improve validity of the study, the co-authors participated in the interviews, approved and elaborated the interview guide (developed and) used in the interviews (the interview guides are available at the end of the document, appendices 1 and 2). Further, they read and discussed the data derived from the interviews several times to enable coding and development of categories and themes (69). Such an analytical approach enhances the reliability of the study. Based on the content analysis, a model of how to distinguish homeopathic aggravations from adverse effects was developed in study II and refined in study III.

To enhance validity and theoretical transparency, the themes and models were sent to the participants for comments and verification. One homeopath strongly disagreed with the model that distinguishes homeopathic aggravation from adverse effect, as he believed that homeopathic treatment did not cause any adverse effects. The majority, however, found the model relevant for clinical practice. This approach enhanced the generalizability of the two studies included in this research plan (69, 100). However, including less experienced homeopaths in the focus group interviews may have revealed other aspects and approaches about the phenomenon in question than the more experienced homeopaths provided.

#### **11.4.2 Cross sectional study**

Aslak Steinsbekk developed the first version of the questionnaire, used in the cross-sectional survey. He used the form for “reporting adverse effects” developed by Statens legemiddelverk (42) as a guide when designing the questionnaire. A small pilot study was performed, and 25 patients who had visited homeopaths received and returned the questionnaire to Steinsbekk. The aim of the pilot study was to measure face, content, criterion and construct validity (see the validity section). The questionnaires were delivered to the author of the present research plan, and some revision of the original questionnaire was made. Demographic data, such as occupation, level of education and marital status was added in the questionnaire and the number of reactions reported after treatment was reduced from five to two.

Interpretation of the findings in cross-sectional studies requires considerable caution, as design allows no conclusions about causal relationships. In study IV the patients reported the reactions after the homeopathic treatment. However, the reasons for the reactions reported remain

unknown. The reactions could be related to the homeopathic remedy, the consultation or other factors, yet unknown. Moreover, as the design merely provides a snapshot of the situation, it is unsuitable for short-term conditions. This situation is called *length-bias sampling*. Length-biased sampling, refers to the fact that cases of long-duration illnesses will be over-represented and cases of short-duration will be under-represented in such surveys (81).

The first step in designing a questionnaire is to have a clear purpose of the study. The topic and the type of information needed must be explicit to keep the questionnaire focused. The questions must measure according to the intentions (face validity), and the wording must be easy to understand and comparable with other studies. The length of the questionnaire must be sufficient to collect the information needed, and short enough to keep the informant focused when filling in the questionnaire (101). Moreover, the wording of the questions and the options available for answering, have a great influence on how people answer the questions.

Almost all questions in a survey could be subject to criticism. However, open versus close questions and the “don’t know” response are the methodological issues discussed in the following. An open-ended question was used when asking for reactions in the questionnaire. (Question 1a: *What was your experience/What was the reaction?*) Open-ended questions allow the respondent to answer the questions in her own words. Such information may be more complete and accurate than information obtained through a more restricted format. It also avoids suggesting or imposing answers the informants may not have considered. Moreover, the open form allows future researchers to create new questions in a retrospective manner on the same subject (102). On the other hand, if the informant does not understand the questions, the answers may not provide the information needed (101). Another drawback is the difficulty of summarizing data, as the researchers must decide how to classify different answers. This may increase the risk of misclassification (80, 101). However, a combination of open-ended and close questions was used in the questionnaire: open-ended for the reactions and structured for the details.

An additional issue to address is the possibility of offering a “don’t know” alternative. Before including this alternative, it is important to consider whether the respondent can actually identify with one of the options given or not (102). Where the respondent has an option, the “don’t know” option should preferably be left out to ensure that the respondent tries to answer according to

what is useful for the study. In the questionnaire used in this survey the “don’t know” option was used twice.

### **11.4.3 Systematic review**

According to the protocol for this research plan, the first task was to perform a systematic review. The candidate spent the first six months performing database searches and methodologically assessing the studies included. The original plan was to include only RCTs. However, a previous researcher at NAFKAM suggested an additional inclusion of observational studies. This was done, and after one year the manuscript was submitted to PLoS ONE (peer-reviewed scientific journal) for publication consideration. The editor of PLoS ONE suggested extension of the searches from 1995-2011 (previous searches were from 2000-2011) and inclusion of German databases. Collaboration with two German researchers was established. To improve the quality of the study, it was decided to perform a meta-analysis of the adverse effects reported in the included studies. One of the German researchers is a statistician who had an appropriate software application to calculate odds ratio and fabricate the results in Forest Plots. The manuscript was revised accordingly. The study became huge, including 82 studies. After another year of reviewing with PLoS ONE, the journal rejected the manuscript. In May 2013, the manuscript was submitted to BMC Complementary and Alternative Medicine. The BMC reviewers suggested including only RCTs to make the study (and article) more transparent and accessible. This advice was also in accordance with that of the commission for this PhD thesis. Article I in this PhD thesis is now a systematic review of RCTs, including 41 studies.

A systematic review must have a clear objective with defined eligibility criteria. A systematic search attempting to identify all studies that would meet the eligibility criteria was applied using the PICO format (see the Cochrane search string in figure 12-1). The first author performed the main searches, and the second author carried out the main German searches. The first and second authors assessed the studies, with assistance from the last author in cases of doubt. To assess the validity of the studies included a risk of bias table was generated. For the RCTs the risk of bias tables included the following criteria: Method (allocation sequence, method of concealment, blinding, loss to follow up), Participants, Intervention, Main findings, Power calculation, Intention to treat analysis and funding. When important information was missing in the studies, the first author was contacted by e-mail. Table 12-1 synthesizes this information from the studies included.

#### **11.4.4 Internal validity**

Validity is an estimate of the accuracy of an instrument or study results. There are two distinct types of validity (70). One is internal validity that is the extent to which the study methods are consistent. The other is external validity that is the extent to which the study results can be applied to a larger population (70). In papers II and III in this research plan, the lay and medical homeopaths applied the same criteria when differentiating homeopathic aggravations from adverse effects, which enhances validity.

There are four main types of internal validity that can be measured and discussed (103). The first concept is face validity, that is the extent to which a method measures according to the intentions (70). A survey is an appropriate method when the main research question is to investigate the prevalence of reactions after treatment in a population (104). The responders in this survey answered in a meaningful way, so the questions used in the questionnaire were relevant for the purpose of the study. This factor enhances the face validity of the survey used in this research plan.

The second concept is content validity, that is the extent to which the questionnaire items cover the research area of interest (70). The questionnaire was designed to capture reactions after homeopathy, and the responders returned relevant answers. However, the questionnaire was designed without a clear question about homeopathic aggravation. An additional question about the concept of homeopathic aggravation, as it was operationalized in this study, would have been helpful to develop criteria to distinguish homeopathic aggravation from adverse effect more precisely (see the discussion in article four).

The third concept is criterion validity that expresses an agreement with a gold standard (70). There is a lack of available, validated questionnaires regarding registration of adverse effects in homeopathy. However, The Norwegian Medicines Agency has a notification form where patients and health care personnel can register adverse effects. This form was used as a model when designing the questionnaire used in this research plan. In addition, homeopath related questions were added to capture conditions specific to homeopathy. Question 5 in the questionnaire is an example: *Did the reaction cause more symptoms than what you consider to be normal?* This question provided information about “homeopathic aggravation, which is a concept specific to homeopathy.

The fourth concept is construct validity that expresses an agreement with other tests available (70). Thus, the concept is understood as agreements with other tests in the field. Only three other studies have investigated the prevalence of homeopathic aggravations and adverse effects in patients using homeopathy. Moreover, only one study used a questionnaire that is published (56). However, due to an inconsistent use of terminology and standardized grading system for both adverse effects and homeopathic aggravations in previous research, it was necessary to establish common terminology for the terms used. To make the results comparable to studies from conventional care, a conventionally established grading system was chosen, which has not been used in previous research on homeopathic aggravations.

#### **11.4.5 Selection bias**

The best way to avoid selection bias in a survey is to invite the entire background population to participate in the study, which was done with the homeopath population as presented in paper IV. It is, however, reason to believe that the participating homeopaths had a positive attitude towards research in general, and this study in particular. This implies that homeopaths with negative research attitudes in general, or negative attitudes towards this research in particular, did not want to participate in the study. In that respect selection bias may have occurred in this research plan, as 64% of the invited homeopaths did not participate.

A random sample is an alternative to ensure that the population studied reflects the background population (101). A common source of selection bias is self-selection. Self-referral of subjects is ordinarily considered a threat to validity because the reasons for self-referral may be associated with the outcome of the study. Even though the inclusion of patients was not self-referred, it is reason to believe that the participants were in favor of homeopathy and wanted to present the treatment as gentle as possible. This may have resulted in an under-estimate of *adverse effects* or an over-estimate of *no reactions* or *improvement of symptoms*. According to the homeopaths, who recruited patients to the survey, some patients did not want to participate in the study. They feared that the findings could result in negative publicity in the media and, thereby, harm homeopathy. It is, therefore, possible that there was a self-selecting bias among the patients. In this case that means that the patients who were the most positive about homeopathy, chose not to participate.

#### **11.4.6 Information bias**

When the groups in a population have been identified, personal information must be collected and used in the analysis. Information bias can be caused by measurement errors in the information needed and may cause bias in estimating an effect or exposure (70). Information bias may occur when the recall time is long (recall bias). It is unlikely that this occurred in study IV, as the participants were asked to report reactions 14 days after the homeopathic consultation. In addition, the participants received the questionnaire at the homeopath office in conjunction with the consultation. Thus, the participants had an increased awareness about reactions after the treatment.

Another possible source of information bias may occur when a participant changes attitude due to inclusion in a research program (101). This change can be grouped into the three categories the cooperative attitude, the defensive or apprehensive attitude, and the negative attitude. The cooperative attitude is characterized as a strong desire to please the researcher, to perform well and with a desire to be positively evaluated by others. Users of homeopathy are likely to have positive attitudes towards homeopathy and be loyal to their homeopaths. This may influence the participants' response by not reporting negative experiences with the homeopathic treatment.

#### **11.4.7 The response rate**

Low response rates are a challenge to the validity of the findings in a study. In paper IV the response rate was 41%, which may be a threat to the generalizability of the findings, because the non-responders may differ in significant ways from those who responded (101), and is a threat to the generalizability of the findings (103). However, the results regarding the prevalence of adverse effects and homeopathic aggravations in the present study, are in line with other studies (5, 56, 64), which suggests that nonresponse bias probably imposes no major threat to the validity of the results (103). Two thirds of the homeopaths invited to participate in the cross-sectional study, had several explanations for not wanting to participate in the present survey. When contacted on the phone, they explained that they had limited access to patients, or that participating was time constraining in a busy daily practice. Others explained that they did not have faith in the project, Many homeopaths find it difficult to accept that homeopathy can cause adverse effects. It seems like this subject is connected with some kind of taboo. However, new information and research about the topic may enforce a change in attitudes, and over time increase the homeopaths'

awareness of possible adverse effects. Such attitude changes have been seen among acupuncturists. Due to unpopular findings, one researcher who investigated possible adverse effects of acupuncture treatment in Norway was excluded from the acupuncture association. Today, more than ten years later, acupuncturists deal with adverse effect of this treatment in a professional way.

#### **11.4.8 Reliability**

Reliability is the ability of a measure to produce equivalent or highly similar results on repeated administrations (101). The reliability of a questionnaire relates to the consistency of the responses across retesting, using equivalent instruments. Repeated testing is the oldest and most conceptual way to establish the reliability of a questionnaire (101). Test-retest was not applied in this survey. Recruiting homeopaths to participate in this survey was challenging for previously explained reasons. In addition, they found it time-consuming to distribute the questionnaires to their patients, which was the reason for not applying the test-retest approach in the present study.

#### **11.4.9 External validity and generalizability**

To enhance external validity, the definitions were sent to the study participants prior to the focus group interviews. All of them agreed on the definitions and the homeopath specific theories applied in this research plan. In addition, the candidate visited a homeopath library in Oslo to gather as much information and knowledge about homeopath specific theories as possible. A comprehensive database search regarding homeopathic aggravation was performed. This search resulted in nine scientific articles about homeopathic aggravations. These articles were used as a fundament to support and validate this research.

In addition, an expert panel (homeopaths) assessed the external validity. This validity reflects the extent to which the homeopaths recognize this research as being relevant to homeopathic practice. A result of this research is two published papers that have been well received in the homeopathic community. Moreover, the feedback from the homeopaths, who the candidate met at international conferences, confirms that this research is both important and pioneering.

Generalizability expresses whether the results found in one population can be true for other populations (70). The main question is whether the findings from this research plan reflect the homeopathic tradition in other countries. Investigating adverse effects and homeopathic aggravations among users of homeopathy has not previously been done in Norway. However,

findings from international studies are in line with the results from the present study (56, 64). The findings from the systematic review conducted in this research plan is in accordance with other studies (54). Only time will show if the criteria to distinguish homeopathic aggravations from adverse effects will be useful for homeopaths in clinical practice. More research into homeopathic practice may reveal other criteria, and adjust them to practice.

### **11.5 Perspective for future research and practice**

The homeopathic community (54) requested more patient safety research in homeopathy, which ultimately would lead to a safety reporting system for adverse effects (105). Data from the research plan presented here suggest guidelines for researchers, applicable when reporting adverse effects of homeopathic treatment. These guidelines are merely an initial step towards improved risk assessment in homeopathy. However, further research is recommended for elaboration and validation purposes. These guidelines are imperative for the comparison of safety data across studies and for patient safety enhancement.

Research suggests an underreporting of adverse effects in homeopathy. One method of encouraging patients to report adverse effects after treatment would be to establish a web-based system. This could be achieved if NHL applies a user–friendly tool on their web page. This step may increase the attention of adverse effects and enhance patient safety.

According to data from this research, several homeopaths believe that homeopathy is free of risk and does not cause adverse effects. This attitude among homeopaths underlines the need for improved awareness of adverse effects and red flag situations in clinical practice. It is, therefore, important that the homeopaths inform their patients to stay in contact if the worsening of symptoms last for more than three days.

Thus, it is imperative that homeopath training increase their attention on the subject and teach the students about red flag situations and possible adverse effects of the treatment. The criteria developed to distinguish between homeopathic aggravations, which may or may not represent the natural course of the disease, and adverse effects will provide a tool within homeopathic theory to facilitate this process.

The current legal regulation for CAM practitioners, including homeopaths, in Norway states that everyone can practice CAM as long as they do no harm. However, findings from this research

plan suggest that it is imperative that the practitioners have both medical and homeopathic skills to safeguard this treatment modality. Consequently, The Alternative Medicine Act (Lov om alternative behandling) should be altered and mandatory requirements about medical and specific skills among CAM practitioners (including homeopaths) should be implemented.

## 12 Supplementary data

An example of a search string for the systematic review is attached below (figure 12-1). The search strategy, using the Boolean operators OR/AND is presented. MeSH and truncation symbols were utilized where available. Titles, abstracts and keywords were searched.

### Search Results

#### Show results in:

Cochrane Reviews [0] Other Reviews [0] **Trials [30]** Methods Studies [0] Technology Assessments [0]

Economic Evaluations [0] Cochrane groups [0]

There are **30** results out of **670154** records for “(#4 AND #9) in Cochrane central Register of Controlled Trials”

### Cochrane Library

#### Current Search History

ID	Search	Hits	Edit	Delete
#1	<a href="#">(homeopathy):ti.ab.kw or (homoeopathy):ti.ab.kw or (homeopathic):ti.ab.kw or (homoeopathic):ti.ab.kw</a>	545	<a href="#">edit</a>	<a href="#">delete</a>
#2	<a href="#">MeSH descriptor Homeopathy explode tree 1</a>	202	<a href="#">edit</a>	<a href="#">delete</a>
#3	<a href="#">(#1 OR #2)</a>	545	<a href="#">edit</a>	<a href="#">delete</a>
#4	<a href="#">(#1 OR #2). from 1995 to 2001</a>	199	<a href="#">edit</a>	<a href="#">delete</a>
#5	<a href="#">(aggravation*):ti.ab.kw or (homeopathic aggravation*):ti.ab.kw</a>	293	<a href="#">edit</a>	<a href="#">delete</a>
#6	<a href="#">(adverse effect*):ti.ab.kw or (safety):ti.ab.kw or (adverse event*):ti.ab.kw or (side effect*):ti.ab.kw</a>	164129	<a href="#">edit</a>	<a href="#">delete</a>
#7	<a href="#">MeSH descriptor Drug Toxicity explode all trees</a>	1259	<a href="#">edit</a>	<a href="#">delete</a>
#8	<a href="#">MeSH descriptor Safety explode all trees</a>	2950	<a href="#">edit</a>	<a href="#">delete</a>
#9	<a href="#">(#5 OR #6 OR #7 OR #8). from 1995 to 2001</a>	40429	<a href="#">edit</a>	<a href="#">delete</a>
#10	<a href="#">(#4 AND #9)</a>	31	<a href="#">edit</a>	<a href="#">delete</a>

[Save Search Strategy](#)

[Clear History](#)

Figure 12-1 The Cochrane Library search string.

Table 12-1 Risk of bias table for the RCTs.

<b>Study</b>	<b>Zabolotnyi (2007) Efficacy of a Complex Homeopathic Medication (Sinfrontal) in Patients with Acute Maxillary Sinusitis: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial</b>
<b>Methods</b>	Complex homeopathic medication ( <i>Sinfrontal</i> ) versus placebo in patients with acute maxillary sinusitis. <i>Allocation sequence:</i> A balanced 1:1 randomization using a block size of four to randomize the patients into the groups, according to a predefined computer-generated list. The block size was unknown to the trial personnel/investigator. <i>Method of concealment:</i> Each investigation site was randomized using two consecutive blocks. <i>Blinding:</i> Patients, investigators and the data monitoring committee were blinded to the treatment allocation. <i>Loss to follow up:</i> One subject in the homeopathy group and six in the placebo group.
<b>Participants</b>	<i>Inclusion criteria:</i> Males and females between the ages of 18-60 with confirmed radiographic diagnosis of acute maxillary sinusitis for the last eight days or longer. <i>Exclusion criteria:</i> Patients with obstructive anatomic lesions in the nose, previous nose surgery, recurrent sinusitis, allergic rhinitis, other lung and upper respiratory diseases, bronchitis, treatment with antibiotics and other medications for sinusitis, hypersensitivity to the investigated drug, cardiovascular diseases or unstable diabetes mellitus, hepatic dysfunction, any alarm symptoms, heavy smoking, pregnancy or breastfeeding women.
<b>Intervention</b>	113 subjects were randomized to receive either <i>Sinfrontal</i> ( <i>Cinnabaris D4, Ferrum D3</i> and <i>Mercurius solubilis D6</i> ) (n=57) or placebo (n=56) which was matched to the active medication regarding colour, smell, taste and viscosity. Subjects in both groups were to take one tablet every hour until the first improvement, followed by two tablets three times a day for 22 days. Additional medication was <i>Paracetamol</i> 500mg for fever (allowed for seven days) and Saline inhalations, if necessary. At the end of the double blind phase, each subject was asked to enter into a prospective eight-week post-treatment observational phase (n=105).
<b>Main findings</b>	The results of this trial appear to demonstrate that <i>Sinfrontal</i> is significantly better than placebo as an effective treatment for acute maxillary sinusitis, both bacterially and virally infected sinusitis confirmed by radiography.
<b>Notes</b>	<i>Power calculation:</i> Performed. <i>Intention to treat analyses:</i> Performed.
<b>Funding</b>	Not reported in publication.
<b>Allocation concealment</b>	A-Clear.
<b>Number of adverse effects</b>	<u>Homeopathy group:</u> 8 cases of gastro-intestinal disorder. Six cases were due to lactose intolerance. Five were classified as mild and three as moderate. <u>Placebo group:</u> One case was classified as mild.
<b>Homeopathic aggravation</b>	Not reported.
<b>Verbatim description</b>	Not reported.
<b>Homeopathic remedy that produced adverse effects or aggravations</b>	Sinfrontal ( <i>Cinnabaris D4, Ferrum D3, Mercur sol D6</i> ).

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## Paper I

Adverse effects of homeopathy, what do we know?  
A systematic review and meta-analysis of randomized controlled trials



Paper II

Is It Possible to Distinguish Homeopathic Aggravation from Adverse Effects?  
A Qualitative Study



Paper III

The Red flag!

Risk assessment among medical homeopaths in Norway: a qualitative study



## Paper IV

Risk in Homeopathy: Classification of Adverse Effects and Homeopathic Aggravations  
– A Cross Sectional study among Norwegian Homeopath Patients



## Appendix 20.1

a) Invitation to participate



## **Kjære Homeopater**

Ved NAFKAM (Nasjonalt forskningscenter innen alternativ og komplementær medisin), er vi i gang med et forskningsprosjekt om homeopati og bivirkninger. Vi vil blant annet gjennomføre en spørreundersøkelse blant 1500 pasienter som oppsøker homeopat for første gang, å spørre dem om deres erfaringer og opplevelse av bivirkninger og førstegangsforverring i forbindelse med behandlingen de fikk hos homeopaten. I denne sammenhengen er det viktig og skille mellom bivirkninger og førstegangsforverring av det homeopatiske middelet.

Så langt viser forskning at bivirkninger opptrer i ca 2-3 % av tilfellene ved homeopatisk behandling. Førstegangsforverring er rapportert i alt fra 10-70% i klinisk praksis.

## **Invitasjon**

I den forbindelse vil vi intervju 10 homeopater for å spørre dem om deres erfaringer med bivirkninger av homeopatisk behandling. Vi inviterer deg med dette til å delta i dette intervjuet. Gjennom intervjuet vil vi forsøke å finne mulige kriterier for hva som skiller disse to fenomenene, og hvordan homeopatene i praksis avgjør når en førstegangsforverring går over til å bli en bivirkning. Intervjuet vil foregå i Oslo i løpet av februar/mars 2011. Vi vil komme tilbake til sted og dato senere.

## **Fokusgruppe intervju**

Vi vil arrangere to fokusgruppe-intervjuer, med 5 homeopater i hver gruppe. Intervjuet vil bli tatt opp på lydbånd, for senere å bli transkribert. Alle deltagerne vil bli anonymisert. Hvert gruppe- intervju vil vare mellom en til to timer. Intervjuet vil foregå som en samtale mellom deltagerne, men forskningslederen vil legge inn noen føringer slik at vi hele tiden er fokusert på de tema som skal belyses. Derfor vil vi be deg om å tenke over følgende:

### **Bivirkninger**

- Hvilke erfaringer har du med bivirkninger av homeopatisk behandling?
- Hvor ofte erfarer du bivirkninger i klinisk praksis.? Hva gjør du da?
- Hvilke rutiner har du hvis/ når det oppstår en slik situasjon? Hvordan informerer du pasientene dine?
- Er det noen sykdommer/lidelser som lettere gir bivirkninger enn andre?

- Er det noen homeopatiske midler som fremkaller dette hyppigere enn andre?
- Hvordan avgjør du om symptomene pasientene får etter behandling er bivirkninger eller førstegangsforverring.

### **Førstegangsforverring**

- Hvilke erfaringer har du med førstegangsforverring av homeopatisk behandling?
- Informerer du alltid/noen ganger/aldri om at pasientene kan få en førstegangsforverring og at dette er en naturlig del av behandlingen?
- Hvor ofte opplever du at pasientene får en førstegangsforverring?
- Hvilke rutiner har du i klinisk praksis som informerer pasienten om dette fenomenet?
- Er det noen lidelser hvor du ser førstegangsforverring hyppigere enn andre?
- Er det noen homeopatiske midler som gir sterkere førstegangsforverring?

### **Praktisk**

Gi beskjed til Trine Stub via e-post, så bestiller NAFKAM flybillett tur- retur Oslo og sender den til deg på e-post. Hvis du må ta buss eller tog så ta vare på billettene så får du refusjon av dine utgifter.

Vi mener denne forskningen er viktig for å sikre pasientsikkerheten ved homeopatisk behandling. Den er også med på å kvalitetssikre homeopatien som medisinsk system. Samtidig er den en del av doktorgradsarbeidet til Trine Stub.

Forskningsprosjektet blir støttet av NHL og håper at du vil delta på dette.

Har du noen spørsmål så kontakt meg på e-post eller telefon: 77 64 92 86

Svarfrist 24. januar

Vennlig hilsen Trine Stub

## Appendix 20.1

### b) Interview guide



## Intervju guide

### Fokusgruppe intervju med homeopater om førstegangsforverringar av homeopatisk medisin og Bivirkningar

#### Introduksjon

##### 1. Velkommen

God formiddag alle sammen. Tusen takk for at dere tok dere tid til å komme til dette gruppe intervjuet i dag [1]. Mitt navn er Trine Stub, jeg er stipendiat ved NAFKAM (Nasjonalt forskningscenter innen alternativ og komplementær medisin). Jeg er utdannet homeopat ved NAN kull III (tror jeg) og har jobbet i privat praksis først i Porsgrunn og så på Statelle siden 1985 (26år).

Jeg har med meg Terje Alræk som er seniorforsker på NAFKAM, og min veileder i dette prosjektet som er en del av mitt doktorgradsarbeid om homeopati og sikkerhet. Han skal være observatør og ordne det tekniske det vil si båndopptakeren. Han vil presentere seg nærmere når vi skal ta en presentasjonsrunde senere.

Vi ønsker å høre om deres erfaringer med homeopatisk førstegangsforverringar. Vi vil gjerne at dere forteller oss hvilke erfaringer dere har med dette fenomenet fra praksis. Vi vil også drøfte, ut i fra deres erfaringer, om homeopatisk behandling har noen bivirkningar. Her vil jeg gjerne presisere at vi ikke skal komme frem til mulig prevalens (utbredelse) av bivirkningar. Men at vi skal gjøre et fagutviklings arbeid hvor vi skal forsøke å skille disse to begrepene fra hverandre basert på deres erfaringer.

Vi har valgt ut dere fordi dere har vært i klinisk praksis i mange år og derfor har praktisk erfaring med disse tingene, som vi nå ønsker og utdype.

Jeg vil dere skal vite at det er ingen svar som er feil, men heller forskjellige synspunkter og erfaringer om disse to fenomenene. Føl dere fri til å si hva dere mener selv om det er forskjellig fra hva andre mener. Vi er interessert i alle kommentarer og husk at vi gjerne vil ha frem alles synspunkter.

##### 2. Innføring i emnet. Hvorfor er dere her

I dag vil vi diskutere og utveksle tanker, meninger og praktiske erfaringer som dere har med førstegangsforverringar og bivirkningar, for deretter forsøke å komme frem til mulige kriterier som skiller disse fra hverandre (fagutvikling). Det vi kommer frem til her vil bli lagt frem for en internasjonal gruppe av homeopater der vi vil forsøke å komme til enighet om disse kriteriene.

##### 3. Kjøreregler i diskusjonen

Før vi starter, la meg foreslå noen ting som vil gjøre diskusjonen mer produktiv. Vær så snill og ta ordet og ikke vær sjenert, men bare en person bør snakke om gangen. Vi vil ta opp dette intervjuet slik at vi ikke mister noen informasjon. Vi er på fornavn med hverandre og i rapporten som skal skrives senere vil vi ikke bruke navnene deres. Slik sett sikrer vi deres anonymitet.

Min rolle her er å stille spørsmål og lytte. Jeg vil ikke delta i samtalen, men ønsker at dere skal snakke åpent med hverandre. Jeg vil stille dere noen spørsmål og lede diskusjonen fra spørsmål til spørsmål. Det er ofte en tendens i en gruppe til at noen snakker mye og andre snakker lite. Men det er viktig at vi hører alles stemme her i dag fordi dere har forskjellige erfaringer. Så hvis det er noen som har mye å dele mye med oss må jeg be deg om at man lar andre også komme til ordet. Og hvis du ikke snakker så mye spør jeg om din mening også.

#### **4. Hvorfor er denne forskningen viktig?**

Hvorfor er denne forskningen viktig. Fordi den er etterspurt i fagmiljøet (British Journal of Homeopathy). Og fordi den er med på å kvalitetssikre homeopatien. Den er også en måte å utvikle faget på. Samtidig er den viktig for pasientsikkerheten og at myndighetene og helsearbeidere inkludert homeopater kan si noe om sikkerheten ved homeopatisk behandling som er basert på forskningen. NHL synes også denne forskningen er viktig, og har derfor støttet dette prosjektet med 30 000 kr fordelt over tre år.

#### **5. Definisjon av begrepene**

Dele ut et ark med definisjonene på. I tillegg kortet mitt og reflekser fra NAFKAM (bra med en aktivitet)

Jeg har sent disse definisjonene til dere på e-post og bedt om at dere kommenterer dem og dette er resultatet. Jeg synes det er viktig at vi går raskt igjennom dem slik at vi alle snakker om det samme.

**Førstegangsforverring.** Både Hahnemann, Kent og Vithoulkas og mange andre store navn innen homeopatien har definert begrepet. Personlig bruker jeg denne definisjonen:

Homeopatisk førstegangsforverring defineres som en forverring av pasientens eksisterende eller tidligere symptomer (som nødvendigvis ikke er tilstede under førstegangskonsultasjonen) og som bryter ut kort tid etter at man har tatt homeopatisk medisin [2]. En slik reaksjon er midlertidig, og blir ansett som en positiv reaksjon som indikerer at en lindrende prosess er satt i gang [3]. Reaksjonen etterfølges av at symptomene forblir som før eller av en bedring av symptomene [2]. De fleste homeopater hevder å ha observert slike reaksjoner i klinisk praksis [4-6].

Faglitteraturen rapporterer at førstegangsforverringer opptrer i alt fra 10 % til 75 % [7] [8] i klinisk praksis.

#### **Bivirkning**

Her bruker jeg definisjonen basert på Statens legemiddelkontroll sin definisjon.

Som bivirkning regnes alle sykdommer eller uønskede og / eller skadelige reaksjoner som oppstår i undersøkelsestiden, uansett sammenhengen med foreskrevet behandling.

For å avgjøre om det er sammenheng med behandlingen brukes tilgjengelig data/opplysninger etter hvilken grad det kan antas å være en sammenheng med behandlingen hos homeopat.

Sannsynlig

Mulig

Ikke sannsynlig

Ingen sammenheng

Ikke mulig å vurdere

Her bruker man tidskriterier for å avgjøre om det er en sammenheng eller ikke.

Som Alvorlige bivirkning regnes bivirkninger som medfører død, livstruende sykdom, vedvarende betydelig nedsatt funksjonsevne eller funksjonskapasitet, sykehusinnleggelse eller forlenget sykehusopphold.

#### Intensitet

Milde: ingen påvirkning av daglig aktivitet

Moderate: påvirkning av daglig aktivitet

Kraftige: ikke i stand til å utføre daglig aktivitet

### **Proving symptomer**

Proving symptom er symptomer pasienten får av et homeopatisk middel som enten er blitt gitt for hyppig og/eller over for lang tid, i en feil fortykning til sensitive personer. Pasienten får symptomer som ligner de symptomene middelet er ment å kurere (ifølge likhetsloven).

Proving: Is the effect caused to the patient by a too frequent ill-timed repetition of the remedy causing pathogenic symptoms of the same remedy that are produced in pure experimentation [9].

### **6. Presentasjon av gruppemedlemmene:**

Jeg vil jeg gjerne at dere presenterer dere for gruppa. Vi starter med å ta en runde rundt bordet.

### **7. Åpningsspørsmålet**

Fortell oss hvem du er, hvor du har praksis og hvor mange år du har vært i praksis. Først vil Terje Alræk presentere seg selv.

Da starter jeg med et spørsmål om førstegangsforverring.

#### Førstegangsforverring

1. Hvor ofte opplever du i din praksis at pasientene dine rapporterer om førstegangsforverring?
2. Informerer du dine pasienter om at dette kan skje, i så fall hvordan informerer du om dette?
3. Litteraturen hevder at det er forskjell på førstegangsforverringene til pasienter som kommer med en
  - a) **akutt lidelse** (kort tid etter inntak av medisinen, og varer bare fra noen timer til en kveld) i forhold til en
  - b) **kronisk lidelse** (forverring av eksisterende symptomer samt oppblomstring av tidligere symptomer, kommer ofte i løpet av de første 14 dagene, kan vare opp til en måned) sammenlignet med pasient som kommer med en
  - c) **kroniske lidelser med akutte topper** (forverringene kommer ofte rundt administrasjon av middelet). Hvis vi antar at dette stemmer, kan dere ta to minutter å tenke litt over dette, så kan vi kanskje starte med forverring hos pasienter som kommer med en akutt lidelse. Hvis dere trenger det ligger det papir og blyanter her på bordet.

### Nøkkelspørsmål

4. De førstegangsforverringene pasientene opplever er de alltid knyttet opp mot pasientens symptombilde, eller er det noen symptomer pasienten kan få som ikke er knyttet opp mot symptombilde? I så fall hvilke? ( hodepine, tretthet). Kan dette i så fall være en mulig bivirkning?
5. Hvordan avgjør du om de forverringene pasienten forteller om, er førstegangsforverringer og ikke en naturlig forverring av sykdommen generelt?
6. Er det noen forandringer pasienten forteller deg om som kan si deg noe om hvilken vei dette går? Mot en bedring eller mot en fortsatt forverring? ( bedre psykisk, fysisk, mer energi, bedre søvn, ”Herings low of cure” eller andre ting?).
7. Som dere vet skal vi forsøke å komme frem til noen mulige kriterier som kan hjelpe homeopatene å differensiere mellom en førstegangsforverring og en bivirkning. Er det noe vi har diskutert så langt som kan bli mulige kriterier?
8. Er det noen homeopatisk midler som gir en sterkere førstegangsforandring enn andre midler?
9. Er det noen sykdommer/tilstander hvor førstegangsforverringer er hyppigere å se enn andre sykdommer?

### Bivirkninger

1. Hvor ofte har du erfart at pasienter har rapportert til deg at de har fått bivirkninger av homeopatisk medisin?
2. Hvis det skulle skje, hva gjør du da? Hvilke rutiner har du?
3. Ber du pasienten kontakte lege? Hvis ja, i hvilke situasjoner ber du pasienten kontakte lege? Har det vært situasjoner der du før oppstart av behandlingen har sent pasienten til lege eller at du i ettertid (etter behandlingen) ser at du burde det? Hvis ja er det noen spesielle sykdommer / pasientgrupper som går igjen?
4. Har du erfart at pasienter får ”**proving symptomer**” av et middel. I tilfelle hvor ofte? I så fall hvilke symptomer var det?
5. Mener du at ”proving symptomer” kan sees på som mulige bivirkninger av homeopatisk medisin?

### Nøkkel symptomer:

6. Vi vet jo alle som sitter her hvor vanskelig det kan være å finne det riktige homeopatiske middelet og ofte kan det være at pasienten trenger flere midler før man kommer i mål. Vithoukaskas har i sin nye bok (Level of Health) beskrevet situasjoner hvor bivirkninger kan oppstå (også andre forskere Rossi /Thompson). Hvis det blir gitt:
  - a) et galt homeopatisk middel / et middel som er nært, men ikke helt perfekt match

- b) Riktig middel, men gal potens eller galt tids- intervall (for hyppig eller vente for lenge med å gi et nytt).
  - c) Seponering av skolemedisinsk behandling
  - d) Har med veldig sensitive personer å gjøre, eller med
  - e) Pasienter med svakt immunforsvar, så kan det oppstå mulige bivirkninger. Hvilke erfaringer har du med dette?
7. Er det noen symptomer/plager som går igjen hos de pasienter som rapporterer om mulige bivirkninger av behandlingen (her mener jeg plager som ikke er en del av førstegangsforverringen).
  8. Hvordan avgjør du om de symptomene pasienten opplever etter homeopatisk medisin er en del av en lindrende prosess /førstegangsforverringer eller er mulige bivirkninger.
  9. Ut i fra det vi har snakket om frem til nå, kan du se for deg noen kriterier som skiller mulige bivirkninger fra førstegangsforverringer?
  10. Er det noen sykdommer hvor du ser mulige bivirkningen av behandlingen oftere enn andre sykdommer? ( ulcerøs colitis, morbus-chron, atopisk eksem, astma).
  11. Er det noen midler som fremkaller mulige bivirkninger oftere enn andre? ( Silicea, Hepar-sulph, Sulphur, Lachesis, Pulsatilla)

#### Avslutningsspørsmål

Hva synes du er det viktigste vi har diskutert her i dag?

#### **8. Avslutning**

Terje, vil du summere opp det viktigste vi har kommet frem til i dag?( to til tre minutter)

#### **9. Etter oppsummeringen:**

Er dette en adekvat oppsummering. Dekker det alt som har blitt snakket om her i dag?

Er det noe vi skulle ha snakket om som vi ikke har diskutert?

#### **10. Refleksjon over intervjuet:** (hvis vi får liten tid, kan jeg sende dette på e-post etterpå)

Var dette en grei situasjon og snakke i?

Hva kunne vi ha gjort annerledes?

#### **11. Hvordan skal intervjuet brukes videre**

Som jeg var litt inne på i innledningen så er dette en del av et prosjekt om homeopati og sikkerhet. Det skal til sammen avholdes to gruppeintervjuer, hvorav dette er det første/andre intervjuet. Intervjuene skal nå transkriberes og skrives ut. Jeg kommer til å sende dere et utkast på det vi har kommet frem til, som dere kan kommentere, og som jeg eventuelt vil justere. Så sender vi det ut til en gruppe av internasjonale homeopater i en Delphi prosess [10]. Denne artikkelen som Terje har skrevet, beskriver hvordan dette vil foregå. (Deler ut artikkelen til Terje). Kort fortalt innebærer det flere e-post runder, hvor man til slutt skal komme til enighet om disse kriteriene som vi er på jakt etter.

Åpne opp for videre kontakt

## 12. Debriefing etter intervjuet

1. Hva var de viktigste temaene/ideene/kriteriene som kom frem i diskusjonen?
2. Hvordan skiller de seg ut fra hva vi forventet?
3. Forskjeller mellom gruppene?
4. Hva skal vi ha med i artikkelen/ tesen
5. Hvilke sitater skal være med?
6. Var det noe uventet som ble belyst. Kom vi frem til noe nytt eller var det som forventet?
7. Skal vi gjøre noe annerledes i det neste intervjuet

### Påminnelser til meg selv

#### Pause

Ta en pause og tenk over svaret. Vi venter til dere er klare til å svare

Hva mener dere andre om dette? Andre meninger?

Det er ingen grunn til å forhaste seg, vi tar den tiden dere trenger

Fortell meg hvorfor det ikke er noe svar til dette spørsmålet

#### Underveis

Vær klar på hva som er fokuset for intervjuet (kriterier). Sammendraget skal dreie seg om det. Notater med følgende i tankene: Et kort sammendrag samt notater for analysen etter intervjuet.

Start sammendraget med det som er viktigst

Skriv ned hva som ikke ble nevnt, men kanskje burde blitt det.

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## Appendix 20.1

### c) Definitions of concepts



## Definisjoner

### Førstegangsforverring

Både Hahnemann, Kent og Vithoulkas og mange andre store navn innen homeopatien har definert begrepet. Jeg har valgt og bruker denne definisjonen [1].

Homeopatisk førstegangsforverring defineres som en forverring av pasientens eksisterende eller tidligere symptomer (som nødvendigvis ikke er tilstede under førstegangskonsultasjonen) og som bryter ut kort tid etter at man har tatt homeopatisk medisin [2]. En slik reaksjon er midlertidig, og blir sett på som en positiv reaksjon som indikerer at en kurativ prosess er satt i gang [3]. Reaksjonen etterfølges av at symptomene forblir som før eller av en bedring av symptomene [2]. De fleste homeopater hevder å ha observert slike reaksjoner i klinisk praksis [4-6].

Faglitteraturen rapporterer at førstegangsforverring opptrer i alt fra 10 % til 75 % [7] [8] i klinisk praksis.

### Bivirkning

Definisjonen er basert på Statens legemiddelkontroll sin definisjon.

Som bivirkning regnes alle sykdommer eller uønskede og / eller skadelige reaksjoner som oppstår i undersøkelsestiden, uansett sammenhengen med foreskrevet behandling.

For å avgjøre om det er sammenheng med behandlingen brukes tilgjengelig data/opplysninger etter hvilken grad det kan antas å være en sammenheng med behandlingen hos homeopat.

Sannsynlig

Mulig

Ikke sannsynlig

Ingen sammenheng

Ikke mulig å vurdere

Her bruker man tidskriterier for å avgjøre om det er en sammenheng eller ikke.

Som Alvorlige bivirkning regnes bivirkninger som medfører død, livstruende sykdom, vedvarende betydelig nedsatt funksjonsevne eller funksjonskapasitet, sykehusinnleggelse eller forlenget sykehusopphold.

## Intensitet

Milde: ingen påvirkning av daglig aktivitet

Moderate: påvirkning av daglig aktivitet

Kraftige: ikke i stand til å utføre daglig aktivitet

## **Proving symptomer**

Proving symptomer er symptomer pasienten får av et homeopatisk middel som enten er blitt gitt for hyppig og/eller over for lang tid, i en feil fortykning til sensitive personer. Pasienten får symptomer som ligner de symptomene middelet er ment å kurere (ifølge likhetsloven).

Proving: Is the effect caused to the patient by a too frequent ill-timed repetition of the remedy causing pathogenic symptoms of the same remedy that are produced in pure experimentation [9].

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## Appendix 20.2

a) Invitation to participate



## **Kjære Lege og Homeopat**

Ved NAFKAM (Nasjonalt forskningscenter innen alternativ og komplementær medisin), er vi i gang med et forskningsprosjekt om homeopati og risiko. Blant annet holder vi på med en spørreundersøkelse blant pasienter som oppsøker homeopat for første gang, hvor vi spør dem om deres erfaringer og reaksjoner etter homeopatisk behandlingen. Vi har også gjennomført to gruppe- intervjuer med klassiske homeopater, hvor vi har spurt dem om hvordan de skiller førstegangsforverring fra bivirkninger av behandlingen. Tidligere forskning viser at bivirkninger opptrer i ca 2-3 % av tilfellene ved homeopatisk behandling. Førstegangsforverring er rapportert i alt fra 10-70% i klinisk praksis. Vi mener det vil være interessant å spørre leger som også er homeopater om hvilke erfaringer de har med risiko knyttet til klinisk praksis.

### **Invitasjon**

Det er pr i dag bare en håndfull personer i Norge med samme bakgrunn som din egen. Vi mener du besitter en unik kompetanse og klinisk erfaring som det er viktig å forske på. I den forbindelse vil vi invitere deg til å delta i et fokusgruppe- intervju. Gjennom intervjuet vil vi forsøke å finne noen kriterier som skiller førstegangsforverring fra bivirkninger og hvordan du i praksis avgjør når en førstegangsforverring går over til å bli en bivirkning. Intervjuet vil foregå i Oslo i slutten av november, eller i begynnelsen av desember 2011.

### **Fokusgruppe intervju**

Vi vil arrangere to fokusgruppe- intervju, med 4 lege- homeopater i hver gruppe. Intervjuet vil bli tatt opp på lydbånd, for senere å bli transkribert. Alle deltagerne vil bli anonymisert. Hvert gruppe- intervju vil vare mellom en til to timer. Intervjuet vil foregå som en samtale mellom deltagerne, men forskningslederen vil legge inn noen føringer slik at vi hele tiden er fokusert på de tema som skal belyses. Vi vil be deg om å tenke over følgende:

#### **Bivirkninger**

- Hvilke erfaringer har du med bivirkninger av homeopatisk behandling?
- Hvor ofte erfarer du bivirkninger i klinisk praksis.? Hva gjør du da?
- Hvilke rutiner har du hvis/ når det oppstår en slik situasjon? Hvordan informerer du pasientene dine?
- Er det noen sykdommer/lidelser som lettere gir bivirkninger enn andre?

- Er det noen homeopatiske midler som fremkaller dette hyppigere enn andre?
- Hvordan avgjør du om symptomene pasientene får etter behandling er bivirkninger eller førstegangsforverring.

### **Førstegangsforverring**

- Hvilke erfaringer har du med førstegangsforverring av homeopatisk behandling?
- Informerer du alltid/av og til/aldri om at pasientene kan få en førstegangsforverring og at dette er en naturlig del av behandlingen?
- Hvor ofte opplever du at pasientene får en førstegangsforverring?
- Er det noen lidelser/ homeopatiske midler, hvor du ser førstegangsforverring mer hyppig enn ved andre lidelser?

### **Andre tema vil være:**

- Erfaring med ”Doctor delay contact” (Forsinket kontakt med helsevesenet).
- Hvordan er det for deg å tilhøre to medisinske paradigmer?
- Hva skiller disse to paradigmene og hva har de tilfelles?
- Hva gjør det med deg som terapeut? Hvordan håndterer du dette i daglig praksis?
- Hva er etter din mening det unike med homeopatien som medisinsk system?

### **Praktisk**

Intervjuene skal holdes i Oslo. Vi kommer nærmere tilbake til hvor, når datoen er fastsatt. Vi håper å få til et intervju på fredag og et på lørdag.

Følgende dato er aktuelle: fredag **18.11** eller fredag **25.11.** eller fredag **02.12.** Alle fredagene kl:**17.30.**

Lørdag **19.11.** Lørdag **26.11.** Lørdag **3.12.** Alle lørdagene kl:**12.00.**

Fint om du svarer til Trine på e-post [trine.stub@uit.no](mailto:trine.stub@uit.no) hvilke av disse datoene som passer (så mange du kan). Vi dekker reiseutgifter samt servering du trenger underveis. Ta derfor vare på kvitteringene. Det blir enkel servering under intervjuet..

Vi mener denne forskningen er viktig for å sikre pasientsikkerheten ved homeopatisk behandling. Den er også med på å kvalitetssikre homeopatien som medisinsk system.

Dessuten er dette et fagutviklings prosjekt. Det er også en del av doktorgradsarbeidet til Trine Stub som er homeopat, akupunktør og forsker. Forskningsprosjektet blir støttet av NHL.

Vi håper at du ser nytten av denne forskningen hvor du også får gleden av å treffe kolleger med samme bakgrunn som deg selv.

Har du noen spørsmål så kontakt Trine på e-post: [trine.stub@uit.no](mailto:trine.stub@uit.no)  
eller telefon: 77 64 92 86 eller mobil: 92 26 75 02

Forskningsgruppen består av: Trine Stub, Terje Alræk og Anita Salamonsen, alle forskere ved NAFKAM.

Hilsen, Trine Stub

(på vegne av forskningsgruppen)



## Appendix 20.2

### b) Interview guide



## Intervjuguide

### Fokusgruppe intervju med lege- homeopater om homeopati og risiko

#### Introduksjon

##### 1. Velkommen

God formiddag alle sammen. Tusen takk for at dere tok dere tid til å komme til dette intervjuet i dag [1]. Mitt navn er Trine Stub, jeg er stipendiat ved NAFKAM. Utdannet homeopat ved NAN kull III og akupunktør fra Norsk Akupunktur skole kull I. Jeg har en master i akupunktur fra Sydney og en Master i Folkehelsevitenskap fra Universitetet i Tromsø. Før jeg kom til Tromsø jobbet jeg i privat praksis først i Porsgrunn og så på Statelle i 23år.

Jeg har med meg Terje og Anita som er forskere på NAFKAM. Terje er min veileder i dette prosjektet som er en del av mitt doktorgradsarbeid om homeopati og sikkerhet. Anita har lang erfaring i bruk av intervjuer som forskningsmetode. Både Anita og Terje skal være observatører og senere bidra til artikkelen som skal skrives på bakgrunn av dagens intervju med dere. De skal også ordne det tekniske, det vil si båndopptakeren. De vil presentere seg nærmere når vi skal ha en presentasjonsrunde senere. Før vi begynner vil jeg be dere om å fylle ut et skjema, så vi får litt informasjon om utdanning og den praksisen der har. ( Deler ut skjema).

##### Start

Vi ønsker å høre om deres erfaringer med **homeopatisk førstegangsforverring**. Vi vil gjerne at dere forteller oss hvilke erfaringer dere har med dette fenomenet fra praksis. Vi vil også drøfte om homeopatisk behandling har noen **bivirkninger**. Vi vil også diskutere andre aspekter av risiko begrepet slik som ” **Doctor deley contact**”, **om pasienter som bryter helt med helsevesenet utgjør en helserisiko**, om **interaksjon** mellom legemidler og homeopatiske midler/urter og hvilke erfaringer dere har med å behandle **sensitive personer**.

Vi har valgt ut dere fordi dere har vært i klinisk praksis som både lege og homeopat og som sådan besitter en unik kompetanse, derfor vil vi gjerne diskutere **hvordan det er å tilhøre to medisinske paradigmer**.

I et **fokusgruppe- intervju** som dette, er det ingen svar som er feil. Vi leter tvert i mot etter forskjellige synspunkter på og erfaringer med temaene som reises. Føl dere fri til å si hva dere mener selv om det er forskjellig fra hva andre mener. Vi er interessert i alle kommentarer og husk at vi gjerne vil ha frem alles synspunkter.

##### 2. Kjøreregler i diskusjonen

Før vi starter, la meg foreslå noen ting som vil gjøre diskusjonen mer produktiv. Vær så snill og ta ordet og ikke vær sjenert, men bare en person bør snakke om gangen. Vi vil ta opp dette intervjuet slik at vi ikke mister noen informasjon. Vi er på fornavn med hverandre og i artikkelen som skal skrives senere vil vi ikke bruke navnene deres eller annen informasjon som kan identifisere dere. Slik sett sikrer vi deres anonymitet.

Min rolle her er å stille spørsmål og lytte. Jeg vil ikke delta i samtalen, men ønsker at dere skal snakke åpent med hverandre. Jeg vil stille dere noen spørsmål og lede diskusjonen fra spørsmål til spørsmål. Det er ofte en tendens i en gruppe til at noen snakker mye og andre snakker lite. Men det er viktig at vi hører alles stemme her i dag fordi dere har forskjellige erfaringer. Så hvis det er noen som har mye å dele med oss må jeg be deg om at man lar andre også komme til ordet. Og hvis du ikke snakker så mye spør jeg deg om din mening også.

#### **4. Hvorfor er denne forskningen viktig?**

Hvorfor er denne forskningen viktig? Fordi den er etterspurt i fagmiljøet (British Journal of Homeopathy). Og fordi den er med på å kvalitetssikre homeopatien. Den er også en måte å utvikle faget på og løfter frem, en i Norge, liten gruppe terapeuter, med en unik kompetanse innen to fagfelt. Samtidig er forskningen viktig for pasientenes sikkerhet og for at myndighetene og andre i helsevesenet kan si noe om homeopatisk behandling som er basert på forskningen. NHL synes også denne forskningen er viktig, og har derfor støttet dette prosjektet med 30 000 kr.

#### **5. Presentasjon av gruppemedlemmene:**

Jeg vil jeg gjerne at dere presenterer dere for gruppa. Vi starter med å ta en runde rundt bordet.

#### **6. Presentasjon av med forskere i prosjektet**

Anita og Terje presenterer KORT seg selv

#### **7. Åpningsspørsmålet**

Fortell oss hvem du er og arbeidet ditt.

Da starter jeg med et spørsmål om førstegangsforverring.

#### **8. Førstegangsforverring**

- Opplever du i din praksis at pasientene dine rapporterer om førstegangsforverring i så fall, hvor ofte?
- Informerer du dine pasienter om at dette kan skje, i så fall hvordan informerer du om dette?

#### **Nøkkelspørsmål**

- Hvordan avgjør du om de forverringene pasienten forteller om, er førstegangsforverring og ikke en naturlig forverring av sykdommen generelt?
- Er det noen forandringer pasienten forteller deg om som kan si deg noe om hvilken vei dette går? Mot en bedring eller mot en fortsatt forverring? (bedre psykisk, fysisk, mer energi, bedre søvn, "Herings low of cure" eller andre ting?).
- "Doctor deley contact " Pasienter som bruker homeopati, fordi de i noen tilfeller oppsøker lege senere enn de ellers ville ha gjort og som sådan kan den homeopatiske behandlingen utgjøre en helserisiko. Hvordan løser du dette?

#### **9. Bivirkninger**

- Har du erfart at pasienter har rapportert til deg at de har fått bivirkninger av homeopatisk medisin?
- Hvis det skulle skje, hva gjør du da? Hvilke rutiner har du?

### **Nøkkel symptomer:**

Vi vet jo alle som sitter her hvor vanskelig det kan være å finne det riktige homeopatiske middelet og ofte kan det være at pasienten trenger flere midler før man kommer i mål. Har du opplevd at pasientene dine har fått bivirkninger av behandlingen hvis du har gitt

- Et galt homeopatisk middel / potens eller tids intervall?
- Seponering av skolemedisinsk behandling, eller ved interaksjon mellom skolemedisin og homeopatisk medisin.
- ”Highly sensitive persons” er kjent fra litteraturen, hvilke erfaringer har du med slike pasienter og hvordan behandler du dem?
- Hvordan avgjør du om de symptomene pasienten opplever etter homeopatisk medisin er en del av en lindrende prosess /førstegangsforverring eller er mulige bivirkninger.
- Ut i fra det vi har snakket om frem til nå, kan du se for deg noen kriterier som skiller mulige bivirkninger fra førstegangsforverring?

### **10. Pasienter som bryter helt med skolemedisinen**

- Noen pasienter bryter helt med skolemedisinen, hva synes/tenker du om det?
- Utgjør bruddet med skolemedisinsk behandling en helse – risiko?
- Hvorfor tror du pasienter velger å gå til deg som både er lege og homeopat?

### **11. Hvordan er det å tilhøre to medisinske paradigmer?**

- Hvordan vil du beskrive det skolemedisinske og alternativ medisinske paradigme? Likheter og forskjeller?
- Hvordan forener du i din praksis disse to verdensbildene?
- Hva gjør det med deg som terapeut?
- Hvordan kommer dette dine pasienter til gode? ( risiko)
- Er det noen ulemper for deg i din yrkesutøvelse å være utdannet innenfor begge disse paradigmene? (hvordan andre leger ser på en lege som er homeopat, evt også hvordan homeopater ser på homeopater som også er leger).

### **12. Kommunikasjon**

- Mange pasienter ønsker å snakke med terapeuten sin om problemer av eksistensiell karakter ofte knyttet til alvorlig sykdom, Hvordan gjør du dette?
- Hvordan kan det homeopatiske intervjuet være med på å åpne opp for en slik

### **Avslutningsspørsmål**

- Hva synes du er det viktigste vi har diskutert her i dag? kommunikasjon? Kan mangel på slik kommunikasjon være en helserisiko for pasientene? Hvordan og hvorfor?

### **8. Avslutning**

Anita / Terje, vil du summere opp det viktigste vi har kommet frem til i dag?( to til tre minutter)

### **9. Etter oppsummeringen:**

- Er dette en adekvat oppsummering. Dekker det alt som har blitt snakket om her i dag?
- Er det noe vi skulle ha snakket om som vi ikke har diskutert?

## **10. Refleksjon over intervjuet:**

- Var dette en grei situasjon og snakke i?
- Hva kunne vi ha gjort annerledes?

## **11. Hvordan skal intervjuet brukes videre**

Som jeg var litt inne på i innledningen så er dette en del av et prosjekt om homeopati og sikkerhet. Det skal til sammen avholdes to gruppeintervjuer, hvorav dette er det første/andre intervjuet. Intervjuene skal nå transkriberes og skrives ut. Analysen gjøres sammen med Anita og Terje. Jeg kommer til å sende dere et utkast på det vi har kommet frem til, som dere kan kommentere, og som jeg eventuelt vil justere. Når artikkelen er ferdig skrevet og publisert, sender jeg den til dere.

Åpne opp for videre kontakt

## **12. Debrifing etter intervjuet**

1. Hva var de viktigste temaene/ideene/kriteriene som kom frem i diskusjonen?
2. Hvordan skiller de seg ut fra hva vi forventet?
3. Forskjeller mellom gruppene?
4. Hva skal vi ha med i artikkelen/ teksten
5. Hvilke sitater skal være med?
6. Var det noe uventet som ble belyst. Kom vi frem til noe nytt eller var det som forventet?
7. Skal vi gjøre noe annerledes i det neste intervjuet

## **Påminnelser til meg selv:**

### **Pause**

Ta en pause og tenk over svaret. Vi venter til dere er klare til å svare

Hva mener dere andre om dette? Andre meninger?

Det er ingen grunn til å forhaste seg, vi tar den tiden dere trenger

Fortell meg hvorfor det ikke er noe svar til dette spørsmålet

### **Underveis**

Vær klar på hva som er fokuset for intervjuet (kriterier). Sammendraget skal dreie seg om det. Notater med følgende i tankene: Et kort sammendrag samt notater for analysen etter intervjuet.

Start sammendraget med det som er viktigst

Skriv ned hva som ikke ble nevnt, men kanskje burde blitt det.

## **Referanser**

1. Rossi E, Bartoli P, Bianchi A, Endrizzi C, and Da Fré M, Homeopathic aggravation with Quintamillesimal Q (or LM) potencies. 2010, Homeopathic Clinic Local Health Authority 2: Lucca.

## Appendix 20.2

### c) Definitions of concepts



## Definisjoner

### Førstegangsforverring

Både Hahnemann, Kent og Vithoulkas og mange andre store navn innen homeopatien har definert begrepet. Jeg har valgt og bruker denne definisjonen [1].

Homeopatisk førstegangsforverring defineres som en forverring av pasientens eksisterende eller tidligere symptomer (som nødvendigvis ikke er tilstede under førstegangskonsultasjonen) og som bryter ut kort tid etter at man har tatt homeopatisk medisin [2]. En slik reaksjon er midlertidig, og blir sett på som en positiv reaksjon som indikerer at en kurativ prosess er satt i gang [3]. Reaksjonen etterfølges av at symptomene forblir som før eller av en bedring av symptomene [2]. De fleste homeopater hevder å ha observert slike reaksjoner i klinisk praksis [4-6].

Faglitteraturen rapporterer at førstegangsforverring opptrer i alt fra 10 % til 75 % [7] [8] i klinisk praksis.

### Bivirkning

Definisjonen er basert på Statens legemiddelkontroll sin definisjon.

Som bivirkning regnes alle sykdommer eller uønskede og / eller skadelige reaksjoner som oppstår i undersøkelsestiden, uansett sammenhengen med foreskrevet behandling.

For å avgjøre om det er sammenheng med behandlingen brukes tilgjengelig data/opplysninger etter hvilken grad det kan antas å være en sammenheng med behandlingen hos homeopat.

Sannsynlig

Mulig

Ikke sannsynlig

Ingen sammenheng

Ikke mulig å vurdere

Her bruker man tidskriterier for å avgjøre om det er en sammenheng eller ikke.

Som Alvorlige bivirkning regnes bivirkninger som medfører død, livstruende sykdom, vedvarende betydelig nedsatt funksjonsevne eller funksjonskapasitet, sykehusinnleggelse eller forlenget sykehusopphold.

## Intensitet

Milde: ingen påvirkning av daglig aktivitet

Moderate: påvirkning av daglig aktivitet

Kraftige: ikke i stand til å utføre daglig aktivitet

## **Proving symptomer**

Proving symptomer er symptomer pasienten får av et homeopatisk middel som enten er blitt gitt for hyppig og/eller over for lang tid, i en feil fortykning til sensitive personer. Pasienten får symptomer som ligner de symptomene middelet er ment å kurere (ifølge likhetsloven).

Proving: Is the effect caused to the patient by a too frequent ill-timed repetition of the remedy causing pathogenic symptoms of the same remedy that are produced in pure experimentation [9].

## **Referanser**

1. European Council for Classical Homeopathy. The Safety of Homeopathy An ECCH Report. In: European Council for Classical Homeopathy; 2009:1-35
2. Thompson E, Barron S, Spence D. A preliminary audit investigating remedy reactions including adverse events in routine homeopathic practice. Homeopathy 2004;93:203-209
3. Endrizzi C, Rossi E, Crudeli L, Garibaldi D. Harm in homeopathy: Aggravations, adverse drug events or medication errors? Homeopathy 2005;94:233-240
4. Popova T. Homeopathic aggravations  
Br Hom J 1991;80:228-229
5. Logan R. The Homeopathic Treatment of Eczema. Beaconsfield, Bucks: Beaconsfield Publishers LTD; 1998
6. Owen D. Principles and practice of Homeopathy. The Therapeutic and Healing Process. London: Churchill Livingstone Elsevier; 2007
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9. Rossi E, Bartoli P, Bianchi A, Endrizzi C, Da Fré M. Homeopathic aggravation: Quintamillesimal, Q (or LM), potencies. Homeopathy 2010;in manuscript

## Appendix 20.3

### a) Information to participating homeopaths





DET HELSEVITENSKAPLIGE FAKULTET

INSTITUTT FOR SAMFUNNSMEDISIN

NAFKAM - NASJONALT FORSKNINGSSENTER INNEN KOMPLEMENTÆR OG ALTERNATIV MEDISIN

Til homeopatene som deltar i denne undersøkelsen. Her er mer informasjon om og hva dere skal gjøre og materiale for studien.

## Pasientsikkerhet ved homeopatisk behandling

Denne pakken inneholder følgende:

### 1. **30 samtykkeerklæringer - 15 til personer under 16 år og 15 til personer over 16 år**

Alle som sier ja til å delta i studien må undertegne samtykkeerklæringen å sende den tilbake til oss sammen med spørreskjemaet.

### 2. **15 spørreskjemaer**

Pasientene skal returnere spørreskjemaet til NAFKAM i vedlagt konvolutt. NB! Husk at du skal fylle inn dato for utlevering av skjemaet, før du gir det til pasienten.

### 3. **15 store konvolutter.**

Du legger samtykkeerklæringen og spørreskjemaet i konvolutten og gir dette til pasientene når konsultasjonen er ferdig.

### 4. **3 registreringskjema til pasienter som vil delta i studien.**

Skriv inn adressen til pasienten og nummeret på spørreskjemaet (se nummeret øverst til høyre på skjemaet). Send inn skjemaet til oss når du har registrert tre - fire pasienter, enten med post (bruk vedlagte konvolutter) eller e-post: [trine.stub@uit.no](mailto:trine.stub@uit.no). For å holde kontroll på hvor mange pasienter du har rekruttert til studien brukes ett av skjemaene til dette (ta gjerne en kopi til eget bruk).

### 5. **1 registreringskjema til pasienter som ikke vil delta i studien.**

Skriv inn dato, kjønn og alder. Skjemaet sendes til oss sammen med registreringskjemaet for de inkluderte pasientene ved studiens slutt.

### 6. **3 små konvolutter.**

Brukes til retur av registrerings skjema.

Les mer på neste side. →

## Introduksjon til pasienten

Det er viktig at du introduserer pasientene til studien med en gang **før** selve konsultasjonen starter. Vi vil gjerne at dere presenterer studien for pasienten omtrent på samme måte, da en standardprosedyre ved presentasjon av studien styrker dens troverdighet. Fint om dere kan si noe i denne retningen:

*"Jeg lurer på om du vil være med i en spørreundersøkelse fra Universitetet i Tromsø, hvor de skal registrere eventuelle reaksjoner av homeopatisk medisin. Jeg som homeopat synes det er kjekt om du vil være med. Spørreskjemaene vil bli behandlet anonymt og det spørres ikke etter fortrolig informasjon mellom deg og meg."*

Så kan du legge til hva det vil innebære og bli med. Slikt som å svare på et spørreskjema 14 dager etter at de har startet med homeopatiske medisin, samt et nytt spørreskjema seks måneder senere.

Vi på NAFKAM sender ut eventuelle purringer og utsendelse av spørreskjema 2 til pasientene.

Tusen takk for at du ble med på dette viktige arbeidet! Alle som deltar vil få informasjon fra studien når resultatene er klare

## Har du noen spørsmål om studien kan du ta kontakte:

Trine Stub  
Stipendiat  
NAFKAM  
Tlf: 77 64 92 86  
E-post: trine.stub@uit.no

Terje Alræk  
Seniorforsker  
NAFKAM  
Tlf: 55 58 61 51  
E-post: terje.alrak@uit.no

**Postadresse:**  
NAFKAM  
v/Trine Stub  
Universitetet i Tromsø  
9037 Tromsø

## Appendix 20.3

### b) Information and consent letter to children







## Appendix 20.3

c) Information and consent letter to adults



*Forespørsel om å delta i forskningsprosjekt*

## PASIENTSIKKERHET VED HOMEOPATISK BEHANDLING

Informasjon

### Bakgrunn

Vi spør deg om å delta i en spørreundersøkelse om homeopati ved Universitetet i Tromsø. I denne undersøkelsen skal vi undersøke om homeopati har bivirkninger eller gir andre reaksjoner. Det vil si en virkning av behandlingen som ingen ønsker. Vi vet fra undersøkelser i utlandet at homeopati gir få bivirkninger, men vi vet ikke om dette stemmer med norske forhold. Derfor spør vi deg som har vært hos homeopat for dine plager, om å delta i denne spørreundersøkelsen.

### Hva innebærer det å delta i prosjektet?

Hos homeopaten vil du få en konvolutt som inneholder et spørreskjema som du skal svare på. Etter seks måneder vil du få tilsendt det samme spørreskjemaet en gang til. Det må også fylles ut og sendes til oss. Svarconvolutt er lagt med. Svarene du sender, blir lest og analysert av forskerne. Forskerne får ikke vite hva du har snakket med homeopaten om, og homeopaten får heller ikke vite noe om dine svar.

### Hva skjer med informasjonen om deg?

Navnet ditt og spørreskjemaet vi får fra deg blir koblet til en tallkode. Tallkoden blir koblet til en navneliste slik at vi kan finne igjen navnet ditt og adressen din. Disse opplysningene blir låst inn i et skap, og bare vi forskere kan låse opp skapet. Svarene vi får fra spørreskjemaene vil bli brukt til å skrive artikler. Artikkene blir publisert, og ingen kan koble deg og de svarene du har gitt i spørreskjemaet til det vi skriver om i artikkene.

### Må du delta i prosjektet?

Nei. Det er frivillig å delta og du kan trekke deg uten å oppgi noen grunn for det. Men det vil være til stor hjelp for oss hvis du blir med.

Hvis du har lyst til å være med i prosjektet, ber vi deg skrive under med navn og dato. Vennligst returner dette sammen med spørreskjemaet.

Med vennlig hilsen  
Trine Stub  
PhD Stipendiat

✂-----

**Jeg vil være med i forskningsprosjektet**

.....  
Dato

.....  
Navn



## Appendix 20.3

### d) Questionnaire



# Spørsmål om reaksjoner etter behandling hos homeopat

Dette spørreskjemaet er en del av et forskningsprosjekt som skal undersøke pasientsikkerhet ved behandling hos homeopat.

Vi har spurt 200 homeopater om å gi dette spørreskjemaet til pasientene sine. Derfor mottar du dette spørreskjemaet i forbindelse med ditt besøk hos homeopaten.

Vi mottar ingen informasjon om deg fra homeopaten, så spørreskjemaet er fullstendig anonymt.

Det er helt frivillig å være med i denne undersøkelsen. Vi håper likevel at du vil ta deg tid til å svare slik at vi får opplysninger fra tilstrekkelig antall personer til å kunne fullføre dette forskningsprosjektet.

Vennligst returner dette skjemaet i vedlagt konvolutt uansett om du har fylt det ut eller ikke.

Jeg ønsker ikke å delta.

## FYLLES UT AV HOMEOPATEN

Dato for pasientens første konsultasjon: \_\_\_\_\_ (dag/mnd/år)

## FYLLES UT AV PASIENTEN

NB! Fylles ut ca. 14 dager etter du har begynt med homeopatisk medisin.

1) **Oppstart på medisin:** \_\_\_\_\_ (dag/mnd/år)

2) **Dato i dag:** \_\_\_\_\_ (dag/mnd/år)

### BAKGRUNNSINFORMASJON OM DEG

3)  Mann  Kvinne

4) **Fødselsår:** \_\_\_\_\_

5) **Nåværende yrke / virksomhet:** \_\_\_\_\_

6) **Yrkesaktiv:**  Ja  Nei

Hvis ja: Heltid/deltid (prosent): \_\_\_\_\_

7) **Attføring:**  Ja  Nei Tidsrom: \_\_\_\_\_

8) **Uføretrygdet:**  Ja  Nei

Tidsrom: \_\_\_\_\_ Helt/delvis (prosent): \_\_\_\_\_

9) **Arbeidsledig:**  Ja  Nei Tidsrom: \_\_\_\_\_

10) **Pensjonist:**  Ja  Nei Tidsrom: \_\_\_\_\_

*Merknader spørsmål 5-10:* \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

### 11) **Sivilstand:**

Enslig

Gift / samboer / registrert partner

Skilt / separert

Enke / enkemann

Bor med to foreldre (gjelder barn)

Bor med én forelder (gjelder barn)

Bor vekselvis hos foreldrene (gjelder barn)

Bor med andre enn foreldrene (gjelder barn)

### 12) **Din høyeste fullførte utdanning:**

Mindre enn 7-årig folkeskole

7-årig folkeskole

Ungdomsskole / Realskole

Videregående skole/Gymnas/Yrkesfaglig utdanning

Høyskole / Universitet inntil 4 år

Høyskole / Universitet mer enn 4 år

### 13. Hvilke plage / sykdom oppsøkte du homeopaten for?

Bruk egne ord og skriv opptil tre plager her:

Plage / sykdom 1: \_\_\_\_\_

Plage / sykdom 2: \_\_\_\_\_

Plage / sykdom 3: \_\_\_\_\_

### 14. Hvor lenge har du hatt plagen / sykdommen?

Skriv antall og sett et kryss

	Antall	dager	måneder	år
Plage / sykdom 1:	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 2:	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 3:	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### 15. Bruker du eller har du brukt medisiner foreskrevet av lege for plagen / sykdommen?

	Ja	Nei	Hvis ja, skriv navnet på medisinen her:
Plage / sykdom 1:	<input type="checkbox"/>	<input type="checkbox"/>	
Plage / sykdom 2:	<input type="checkbox"/>	<input type="checkbox"/>	
Plage / sykdom 3:	<input type="checkbox"/>	<input type="checkbox"/>	

### 16. Hva var homeopatens råd til deg om denne medisinbruken?

- Ingen oppfordring fra homeopaten om å endre bruk av medisinen(e).
- Homeopaten oppfordret deg til å ta dette opp med legen din for eventuelt å redusere eller endre bruk av medisinen(e).
- Homeopaten oppfordret deg til å redusere eller endre bruk av medisinen(e).
- Homeopaten tok ikke dette opp med deg.

### 17. I hvor stor grad påvirket plagen / sykdommen din daglige aktivitet FØR du oppsøkte homeopat?

	Ingen påvirkning av daglig aktivitet	Påvirket daglig aktivitet	Var ikke i stand til å utføre daglig aktivitet
Plage / sykdom 1:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 2:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 3:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### 18. I hvor stor grad påvirker plagen / sykdommen din daglige aktivitet I DAG?

	Ingen påvirkning av daglig aktivitet	Påvirker daglig aktivitet	Ikke i stand til å utføre daglig aktivitet
Plage / sykdom 1:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 2:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plage / sykdom 3:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## REAKSJONER

Vi er interessert i hvilke reaksjoner du har hatt i tiden **etter** at du tok homeopatisk medisin. Vi ber deg om å skrive ned alle reaksjoner, uansett hva du mener grunnen til reaksjonene kan være.

Vi har satt av plass til å beskrive to reaksjoner i spørreskjemaet. Legg ved ekstra ark hvis du har flere reaksjoner eller trenger mer plass.

Jeg har ikke hatt noen reaksjoner. Da kan du stoppe her, takk for din tid og hjelp!

### Reaksjon 1

1a) Hva opplevde du / hva var reaksjonen?

*Skriv her:*

1b) Hvor lenge varte reaksjonen? *Skriv antall timer / dager/ uker*

Antall  timer

Antall  dager

Antall  uker

1c) Hvor lang tid etter at du tok homeopatisk medisin kom reaksjonen?

*Skriv antall timer / dager/ uker*

Antall  timer

Antall  dager

Antall  uker

1d) Hvordan påvirket reaksjonen din daglige aktivitet?

Ingen påvirkning av daglig aktivitet

Påvirket daglig aktivitet

Var ikke i stand til å utføre daglig aktivitet

1e) Var reaksjonen slik at du fikk sterkere plager enn det du bruker å ha?

Ja  Nei  Vet ikke

1f) Var reaksjonen av en slik art at du gjorde noe for å dempe den?  Ja  Nei

*Hvis ja, hva gjorde du? Du kan sette flere kryss.*

Tok medisin / homeopatisk middel - *Skriv hva du tok her:*

Oppsøkte lege

Sov / hvilte / slappet av

Trente / gikk tur / mosjonerte

Annet, hva gjorde du?

*Skriv her:*

1g) Knyttet du reaksjonen til medisin homeopaten gav deg?

*Hvis ja, beskriv kort:*

Ja  Nei  Vet ikke

## Reaksjon 2

2a) Hva opplevde du / hva var reaksjonen?

*Skriv her:*

2b) Hvor lenge varte reaksjonen? *Skriv antall timer / dager/ uker*

Antall  timer

Antall  dager

Antall  uker

2c) Hvor lang tid etter at du tok homeopatisk medisin kom reaksjonen?

*Skriv antall timer / dager/ uker*

Antall  timer

Antall  dager

Antall  uker

2d) Hvordan påvirket reaksjonen din daglige aktivitet?

Ingen påvirkning av daglig aktivitet

Påvirket daglig aktivitet

Var ikke i stand til å utføre daglig aktivitet

2e) Var reaksjonen slik at du fikk sterkere plager enn det du bruker å ha?

Ja    Nei    Vet ikke

2f) Var reaksjonen av en slik art at du gjorde noe for å dempe den?  Ja  Nei

*Hvis ja, hva gjorde du? Du kan sette flere kryss.*

Tok medisin / homeopatisk middel - *Skriv hva du tok her:*

Oppsøkte lege

Sov / hvilte / slappet av

Trente / gikk tur / mosjonerte

Annet, hva gjorde du?

*Skriv her:*

2g) Knyttet du reaksjonen til medisin homeopaten gav deg?

*Hvis ja, beskriv kort:*

Ja

Nei

Vet ikke

***Takk for din tid og hjelp!***

Vennligs returner dette skjemaet i vedlagt konvolutt uansett om du har fylt det ut eller ikke.

Trine Stub, PhD stipendiat

Terje Alræk, Seniorforsker

Jianping Liu, Seniorforsker

Marja Verhoef, Seniorforsker



## Appendix 20.3

e) English translation of the questionnaire



## Questions about reactions following homeopathic treatment

This questionnaire is part of a research project with the aim of analyzing patient safety connected to homeopathic treatment.

We have asked 200 homeopaths to give this questionnaire to their patients. That is why your homeopath has given you this questionnaire.

We receive no personal information from your homeopath, which ensures you complete confidentiality.

Participation is voluntary. Nevertheless, we hope that you will take your time answering the questions, so that we get information from an adequate number of people who will enable us to complete our research project.

Please return this questionnaire in the reply envelope enclosed, regardless of whether you have answered the questions.

I don't want to participate.

### TO BE COMPLETED BY THE HOMEOPATH

The date of the patient's first consultation (date/month/year)

### TO BE COMPLETED BY THE PATIENT

NOTE: To be completed 14 days after you started on homeopathic medication.

- 1) Started on medication: (date/month/year)  
 2) Today's date: (date/month/year)

### PERSONAL DATA

3) Male Female Boy younger than 18 Girl younger than 18

4) Year of birth:

5) Present occupation:

6) Do you work? Yes No

If yes: Full time/Part time (percent) \_\_\_\_\_

7) Rehabilitation: Yes No Period:

8) Disabled: Yes No

Period: Fully/Partly (percent)

- 9) Unemployed            Yes            No            Period:  
 10) Retired                Yes            No            Period:

Comments to questions 5-10:

- 11) Marital status

Single  
 Married/Cohabitant/Registered partner  
 Divorced/Separated  
 Widow/Widower  
 Living with two parents (for children)  
 Living with one parent (for children)  
 Living with both parents alternately (for children)  
 Living with other than the parents (for children)

- 12) Your highest level of education completed

Less than 7 years of primary school  
 7 years of primary school  
 Lower secondary school  
 Upper secondary school/Vocational school  
 Highschool/University, maximum 4 years  
 Highschool/University, more than 4 years

13. Give an account of the kind of illness/disease that made you see the homeopath. In your own words, describe maximum three kinds of illnesses.

Illness/Disease 1:  
 Illness/Disease 2:  
 Illness/Disease 3:

14. For how long have you suffered from this illness/disease?

*List the number and check one of the boxes*

	Number	Days	Months	Years
Illness/Disease 1:				
Illness/Disease 2:				
Illness/Disease 3:				

15. Do you use or have you used medication for your illness/disease prescribed by a doctor?

	Yes	No	<i>If yes, provide the name of the medication:</i>
Illness/Disease 1:			
Illness/Disease 2:			
Illness/Disease 3:			

16. What kind of advice did the homeopath give you regarding this medication?

No advice from the homeopath on changing the use of the medication(s).

The homeopath advised you to discuss this matter with your doctor with the aim of possibly reducing or changing the use of the medication(s).

The homeopath advised you to reduce or change the use of the medication(s).

The homeopath did not discuss this matter with you.

17. To what extent did the illness/disease affect your daily activities PRIOR TO seeing the homeopath?

Indicate using a number on a scale from 1 to 4 where 1= No influence of daily activities, and 4 = Unable to perform daily activities.

Illness/Disease 1:

Illness/Disease 2:

Illness/Disease 3:

18. To what extent does the illness/disease affect your PRESENT daily activities?

Indicate using a number on a scale from 1 to 4 where 1= No influence of daily activities, and 4 = Unable to perform daily activities.

Illness/Disease 1:

Illness/Disease 2:

Illness/Disease 3:

## REACTIONS

We are interested in knowing what kind of reactions you have experienced **after** having taken homeopathic medication. Please note all kinds of reactions, regardless of your own opinion about the cause.

This questionnaire allows for description of two different kinds of reactions. Please add an extra sheet of paper if you have experienced additional reactions, or if you need more space.

I have not experienced any reaction. You have completed the questionnaire. Thanks for your help!

### Reaction 1

1a) What did you experience/What was the reaction?  
*Give a brief description*

1b) For how long did the reaction last?



days  
weeks

2d) How did the reaction affect your daily life?

No effect

Some effect

Unable to perform daily activities

2e) Did the reaction cause more pain than what you consider to be normal?

Yes

No

Don't know

2f) Did you do anything to lessen the reaction? Yes No

*If yes, what did you do? Du may choose more than one option.*

I took medication/homeopathic remedy – *please note what you took:*

I visited my doctor

I slept/relaxed/calmed down

I exercised/went trudging/went for a walk

Anything else, what did you do?

*Give a brief description.*

2g) Did you connect the reaction to the homeopathic medication?

*If yes, give a brief description.*

Yes No Don't know

Thanks for your help!

Please return this questionnaire in the reply envelope enclosed, regardless of whether you have answered the questions.

Trine Stub, PhD candidate

Terje Alræk, Senior researcher



## Appendix 20.4

Approval from Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)





<b>Region:</b> REK nord	<b>Saksbehandler:</b> Øyvind Strømseth	<b>Telefon:</b> 77620753	<b>Vår dato:</b> 19.09.2011	<b>Vår referanse:</b> 2010/3379/REK nord
			<b>Deres dato:</b>	<b>Deres referanse:</b>
Terje Alræk Forskningsparken			Vår referanse må oppgis ved alle henvendelser	

### **Vedr.: Pasientsikkerhet ved behandling hos homeopat**

Viser til vedtak av 15.4.2011. Ved en feil ble godkjenningen gitt til 1.11.2011, det riktige skulle være 15.8.2013. Dette er rettet opp nedenfor, og dette vedtaket trer i stede for vedtak av 15.4.2011.

### **Pasientsikkerhet ved behandling hos homeopat.**

Vi viser til tilbakemelding av 29.3.2011 vedlagt forespørsel.

I forespørselen er det inntatt følgende setning: "Svarer du på, og sender inn begge spørreskjemaene vil du være med i en utlodning av en iPad touch 32gb." Dette er ikke tidligere omhandlet i søknaden og ordningen kan derfor ikke aksepteres. Setningen må fjernes fra forespørselen.

Etter fullmakt er det fattet slikt

### **Vedtak:**

*Med hjemmel i helseforskningsloven § 10 og forskningsetikkloven § 4 godkjennes prosjektet.*

Før prosjektet kan igangsettes må det sendes inn revidert informasjonsskriv i tråd med komiteens merknader.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK. Vi gjør oppmerksom på at hvis endringene er vesentlige, må prosjektleder sende ny søknad, eller REK kan pålegge at det sendes ny søknad.

Det forutsettes at forskningsdata oppbevares forskriftsmessig.  
Godkjenningen gjelder til 15.8.2013.

Prosjektleder skal sende sluttmelding i henhold til helseforskningsloven § 12.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. forvaltningsloven § 28 flg. Eventuell klage sendes til REK Nord. Klagefristen er tre uker fra mottak av dette brevet.

<b>Besøksadresse:</b> TANN-bygget Universitetet i Tromsø 9037 Tromsø	<b>Telefon:</b> 77646140 <b>E-post:</b> rek-nord@fagmed.uit.no <b>Web:</b> <a href="http://helseforskning.etikkom.no/">http://helseforskning.etikkom.no/</a>	All post og e-post som inngår i saksbehandlingen, bes adressert til REK nord og ikke til enkelte personer	Kindly address all mail and e-mails to the Regional Ethics Committee, REK nord, not to individual staff
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Vi ber om at alle henvendelser sendes inn via vår saksportal: <http://helseforskning.etikkom.no> eller på e-post til: [post@helseforskning.etikkom.no](mailto:post@helseforskning.etikkom.no)

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

May Britt Rossvoll  
sekretariatsleder

Øyvind Strømseth  
seniorrådgiver

Kopi til: [vinjar.fonnebo@uit.no](mailto:vinjar.fonnebo@uit.no)

