

ORIGINAL PAPER

The pitfalls of clinical case research: lessons from the Delphi Project

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Delphi is a project to make high-quality cases treated with homeopathy available for study. The project encountered a number of major difficulties including small numbers of cases submitted, ethical problems and problems of analysis. The nature of these problems and possible solutions are discussed. *Homeopathy* (2004) 93, 21–26.

Keywords: homeopathy; clinical case research; ethics; diagnostic instruments

Introduction

Do we need clinical case research?

In the last decade, homeopathy has found itself in an unexpected position. Fundamental research increasingly shows that homeopathy is not nonsense. Observational outcome studies clearly show the benefits of homeopathic treatment. Yet, formal proof of clinical efficacy remains elusive. Reports of clinical trials where homeopathic remedies fail to confirm the effects we see in everyday practice have been published and met with a lot of criticism within the homeopathic community. The selection of homeopathic medicines is often simplified in such studies. This makes it easier to design a methodologically correct randomised clinical trial (RCT). However, the selection process of homeopathic remedies in practice is different. It is, therefore, important to remember that the RCTs do not always study the same thing as observational outcome studies. We may prefer the positive results of outcome studies to the disappointing news from some recent RCTs. But on closer examination, both are of limited value as instruments for the improvement of homeopathy. Neither offer us

practical and reliable feedback on what we are doing wrong and what right.

It seems inevitable that in order to learn lessons that are of use in daily practice, we must study daily practice. The Delphi Project was started in 1997 with the basic idea of gathering homeopathic case reports and making them available for comparison and study. This article describes problems we encountered, and answers we found. It also contains a warning. Clinical case research is complex and multifaceted, and every facet needs to be thoroughly addressed. Many case research projects have struggled and failed. We hope that by reporting the findings of the Delphi project we may inspire homeopathic prescribers to join our efforts, and inspire other projects to revise their strategies and succeed.

The start of a clinical case research project

The first attempt was made to establish Delphi as a project for clinical case research at a meeting in 1997. Most attention was given to identifying criteria for the quality of case descriptions and to ways of prompting homeopathic prescribers to participate and submit cases to the Delphi library. Several existing lists of case criteria were studied. It was found that even in this relatively small and cohesive group, defining criteria for case reporting was difficult. We agreed however, that the users of Delphi cases would all be experienced prescribers. The basic criterion was that the case be described in such a way that the readers could make their own decision about the quality and usefulness of

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Received 1 August 2003; revised 28 September 2003;
accepted 6 October 2003

the case. All participants felt comfortable with an established set of rudimentary criteria. These are presented in Table 1.

After this meeting the Delphi Project was presented at a series of seminars and congresses, and met with very favourable responses. However, the project did not move forward, and despite numerous promises, very few cases were submitted during the 3 years that followed. It became clear that more energy, time and focus were required to expand the project.

What did we learn?

There was plenty of goodwill, many people honestly and seriously promised to contribute. Once we had decided on the basic criteria, we felt they were applicable for all types of homeopathy, regardless of school or orientation. But we learned that presenting the project and having people understand and support our goals, was insufficient for the project to succeed.

What do we want from clinical case research?

We originally modelled the Delphi Project on successful local study groups, with informal research goals and a strong cohesion often based on long-term collaboration between colleagues. It became apparent that this model did not work among the broader community interested in the Delphi Project. The fundamental principle that careful study of case histories was useful for improving homeopathy was shared by everybody, but focuses differed widely. Some people gave great attention to problems, such as dishonest case reports, or reports too brief or too biased to be useful. Others gave great attention to how to use the case reports as learning tools. Comparing all the feedback we received allowed us to identify a number of problem areas and several learning strategies.

What did we learn?

Although people were enthusiastic about the Delphi Project, they had different views on the goals it should have, and different expectations about the problems it would have to address.

How to design a project

We spoke to several experts from the homeopathic and other scientific communities. They indicated that we needed to describe our goals and procedures more explicitly. In preparation for a meeting in 2001, a study summarising the results of the feedback from participants in the project and the discussions with experts was presented. This outlined the challenges a project in clinical case research could expect to encounter.¹ In addition, input from clinical epidemiology led to a more structured description of different approaches to clinical case research in homeopathy. From these sources, three approaches to clinical case research in homeopathy were recognised. They can be understood as three stages of a scientific process, and are described below (Organising the challenges).

What did we learn?

We learned that a large international project requires an explicit description. We also learned that the accumulated feedback from participants and experts could be condensed into a useful overview of research strategies and potential problems.

Ethics: an underestimated problem

Although few homeopathic prescribers seemed to have great concerns about ethical issues, the founding team of Delphi expected them to become important, and professional advice was sought. The outcome was more complicated than we had anticipated. Besides ethical issues concerning informed consent and confidentiality, legal obligations with regards to gathering, storing and sharing confidential information were found. This was complicated by the fact that regulations are not consistent in all countries of the European Union, and great differences exist between countries on different continents. An unexpected problem was the potential liability of the Delphi Project for any real or perceived damage related to its activities. Stories of such liabilities leading to considerable indemnities being paid for breaches of confidentiality in the USA stressed the seriousness of this topic.

Legal and ethical matters demanded a lot of attention and considerably slowed down the progress

Table 1 Basic criteria for cases

<i>1. Treatment with one single remedy</i>	<i>2. Stable improvement of the patient</i>	<i>3. Not against Hering's rule</i>	<i>4. Relevant duration of follow-up</i>	<i>5. It is evident that it was a homeopathic cure (case mix factors)</i>
Evaluation is most important and most feasible for single remedy cases	A stable state of improvement has been reached, with special interest for the main complaints and the general state of well-being	During the period of observation there should not be an aggravation or deterioration of the system	A duration of follow-up that is meaningful for the condition treated	Other treatments, and important changes in the circumstances of the patient have to be described

of the Delphi Project. Eventually, contributions from Professor JKM Gevers (Amsterdam University) and Professor AJT George (Imperial College, London) helped find practical approaches to these issues. Professor George presented a lecture on the ethical aspects of research in homeopathy during a Satellite Congress on clinical case research in 2003.²

What did we learn?

Legal and ethical issues play a major role in any research, including homeopathy. They need to be addressed in the early stages of any research project. Failure to do so may not only hamper the progress of a project, it may also cause unexpected liabilities for the project and its participants.

Organising the challenges

Clinical case research in homeopathy was found to consist of three consecutive stages, each stage having its own prerequisites. It seems unlikely that any one stage can be successfully developed independent of the others. Participants often focused primarily on one stage of the process, describing how Delphi cases could benefit them. Many wanted to read good, reliable cases, which we came to regard as the qualitative stage of research. Others wanted to compare cases for different remedies and conditions, a semiquantitative approach. Yet others hoped that case series may be of use for statistical analysis, a quantitative approach. The issues that came up while working on the Delphi Project will now be described according to these stages.

Challenges of the qualitative stage

Usually cases are treated as examples, and studied without a real methodological strategy. Readers may remember some interesting qualities of a case, or may think of one of their own unsolved cases that resembles the case described. This is most often what homeopathic prescribers have in mind when they think of clinical case research. This qualitative stage concerns the case descriptions themselves, and the issues with regard to reliability, usefulness and ethics.

All case research projects in homeopathy start with a group of people deciding what the criteria for admission of cases will be. Many projects never get beyond this stage, because the criteria for admission often reflect homeopathic 'beliefs'. Strict criteria increase the workload of authors, and retrospective case descriptions often cannot meet the requirements. Ideals and practicality are in conflict, and discussions on criteria become endless. Choices have to be made according to the objectives of the specific project. A number of basic criteria were identified to prevent less useful cases from entering the Delphi project (Table 1).

Completeness of case descriptions

Completeness is as difficult as the criteria. Some take the view that only complete transcriptions or recordings are good enough. Others state that only information that was relevant for the prescription needs to be recorded. Here, too, ideals and practicality conflict. The Delphi Project holds the view that 'sufficient formulation' of a case will enable the homeopathic prescriber to judge whether the case description suits his or her needs. Still, in the peer review process that is described below, there were constant requests for precise guidelines. This may well be an indication that clinical case research will not flourish unless it is done within a more or less coherent community.

Truthfulness of case descriptions

Problems concerning truthfulness may vary from intentionally fraudulent case reports to unintentional forms of bias from prescriber and/or patient. In the Delphi Project the signature of the patient confirming correctness of the description was seen as a step forward. However, when testing this procedure, we found that patients occasionally do not remember having said or done things several years ago, and they may prefer that certain information be deleted, even though it was written down verbatim at the time. Observations that prescribers prefer not to mention to the patient may also be a problem, especially if this information led to a successful treatment. This dilemma is well known in psychiatry. Of course, intentionally hiding recorded information from the patient is ethically questionable.

Copyright

For some people, presenting cases at seminars is a significant source of income. They may be willing to submit cases for research, but may not accept that others use their cases for teaching purposes or publication. Just like legal and ethical matters, copyright issues need to be addressed explicitly.

Incentives

Researchers tend to overestimate the number of cases they will be able to include in a study. In statistics this has come to be called Lasagna's Law. Clinical case research in homeopathy is no different. It is usually not a problem to convince people of the usefulness of the research, and many people promise support and contributions. Usually, lack of time and other socially acceptable reasons are brought forward to explain failure to deliver. When speaking with participants about why they did not submit cases, deeper motives are often uncovered. Feelings of inadequacy, disappointment about cases that seemed to do well and then deteriorated, and being intimidated by other people's work are often mentioned. As reported below under 'Test Run', people eventually submitted cases when the survival of the Delphi Project was at stake, and

probably did so for reasons of personal sympathy and support. Many suggested incentives and rewards (for example, financial or social) do not address these hidden motives and inhibitions. The homeopathic community should invest resources in exploring this major barrier to the success of essential research.

Formal case series

Trevor Thompson suggests integrating concepts from qualitative research into homeopathic clinical case research. He points out several problems common to many homeopathic case descriptions, including different forms of bias, and the lack of objective evidence such as questionnaire responses, laboratory findings and reports from others than the author.³

Legal and ethical issues

Processing and presenting detailed homeopathic case reports involves dealing with highly confidential data. Concealing basic information, such as names, dates and places, does not necessarily prevent traceability. Fully informed consent implies that the patient is aware of everything that is going to happen to his data, and of every consequence this may have for him. These conditions cannot easily be met. On the other hand, sharing a case history in order to help a colleague with a similar case is acceptable good clinical practice. The obligation to confidentiality remains: cases can only be shared for good reasons, within a defined group of colleagues. The definition of the group however poses problems. In some western European countries, prescribers without statutory registration may be part of such a group. In southern Europe, this may be different.

Creating a database of cases, exchanging them through a central hub and publishing them are activities that require a formally described research project, and certainly require the approval of a medical ethics committee. The qualitative stage of research of the Delphi Project, based on the idea of a case exchange hub can be partly realised within formal legal and ethical boundaries.

What did we learn?

We learned that the ideal case description does not exist, and choices must be made according to the objectives of the research. Excessively idealistic criteria for inclusion of cases create a hurdle too high for participants. The reasons that prescribers submit much less material than they promise go beyond a lack of time and other socially acceptable motives. We also learned that legal and ethical requirements set limitations to our original plans for the qualitative stage.

Challenges of the semiquantitative stage

In the semiquantitative stage of research, cases are compared to find common aspects. These common aspects may then become diagnostic instruments for prescribing a certain remedy. Much of the information in our materia medicas and repertories as well as in recent literature is based on a semiquantitative approach, but it is rarely possible to verify by what procedures, and based on which material, conclusions were reached. Extensive and reliable case descriptions, meeting the specifications for the qualitative stage of research, are needed for research in this stage. The original case descriptions should be available for verification. Unsuccessful cases also play a role in this stage, in order to know which information predicts failure of certain prescriptions, and in order to estimate how reliably other information predicts success.

Methodology

To improve the reliability of the semiquantitative stage, we need clear and comprehensible descriptions of how and why conclusions were reached. Much can be learned from the methodologies developed in qualitative research, these are usually based on case descriptions as detailed as those used in homeopathy. In this stage, selection bias is an interesting issue. We need to select specific cases in order to find assumed common aspects, a 'best case series' approach. On the other hand, selecting only cases that support a certain assumption may result in unreliable prescribing indications. These will eventually be unveiled in the disappointing RCTs as described in the introduction. Assumed common aspects of remedies must not only be correctly derived from the material available but also be useable in daily practice, an important asset for any diagnostic instrument. The presence or absence of the aspect in a new case should be easy to confirm or dismiss. Systematic evaluation of the practicality of prescribing indications is an aspect of the semiquantitative stage that is often neglected. The semiquantitative stage is only possible in a limited form until it is described as a formal research project with approval from medical ethics committees.

What did we learn?

Prescribing indications for homeopathic medicines can be seen as diagnostic instruments, and evaluated as such. Their reliability and practicality require systematic evaluation.

Challenges of the quantitative stage

The quantitative stage comprises the formal validation of the prescribing indications developed in the semiquantitative stage. It should lead to more accurate

repertories and materia medica. In this stage, information about remedies is expressed in quantitative, statistical terms.

Methodology and practical considerations

In the Delphi brochure, the statistical concepts of sensitivity and specificity of diagnostic instruments were presented as tools that could be used in homeopathy. Recently, likelihood ratios have been proposed as being more suitable.⁴ As underlined by the same group, the quantitative stage is a huge task. Producing reliable estimations of likelihood ratios, sensitivity and specificity of homeopathic prescribing indications may require evaluation of thousands of cases.

It should be underlined that the practicality discussed above is of great importance here. Clear and practical prescribing indications make for better diagnostic instruments, with less false-negative and false-positive outcomes. The qualitative and semiquantitative stages are essential before meaningful statistical analysis can be applied.

Legal and ethical issues

The quantitative approach will require the availability of many detailed case descriptions for future reference and comparison, and therefore solid logistical organisation. Handling this amount of confidential data may be subject to specific regulations which may vary between countries.⁵ This stage can only be successfully realised in the form of a well-described research project, approved by a multicentre research ethics committee.

What did we learn?

The quantitative research stage needs to be built on solid work at the qualitative and semiquantitative stages. Making cases and the semiquantitative assumptions available for future reference requires solid organisation of the project.

The role of unsuccessful cases

The role of unsuccessful cases in clinical case research requires special consideration. Any estimate of the usefulness of diagnostic criteria demands the comparison between successful and unsuccessful cases. Publishing an unsuccessful case is more difficult than publishing a successful one. Successful case descriptions are usually modelled on the theories on which the prescription was based. Successful cases may be more comforting, but unsuccessful cases are indispensable for estimating the reliability of our prescribing indications, and their practical usefulness. I know of no project that has systematically studied unsuccessful cases in homeopathy. No progress beyond the qualitative stage of clinical case research can be made until

we develop a way of using unsuccessful cases for scientific evaluation. Obviously, an atmosphere of mutual respect is essential for such work.

Testing a clinical case research project

After discovering that legal and ethical issues were a big hurdle to our original plans, we decided to do a 'test run'. We wanted to find out if cases would actually be submitted, whether or not they would be useful, and how the confidentiality aspects would work in practice. We decided we would continue the Delphi Project only if we received at least 30 cases in total from at least 15 different prescribers, in the 3 months starting from 1 October 2001. This proved to be easier than expected. However, the stream abruptly dried up again after 1 January 2002! Apparently the desire to see the project continue had been the primary motive for submission. The cases received could not be distributed outside the Delphi project, although there were several requests, because of unresolved legal and ethical problems. As expected, cases were reported in very different formats, and it was difficult to judge their usability according to explicit criteria. We therefore decided to have participants of the Delphi community evaluate each others cases anonymously, a peer review procedure.

Peer review

The feedback from peers was as diverse as the case descriptions themselves. Many reviews were friendly and uncritical, even of cases that did not actually meet some basic criteria described above. Some reviews were unfriendly, almost hostile, but with little advice as to how the case description could be improved. Several reviewers gave critical comments in great detail, and these were the most helpful. The authors of the latter were mostly experienced editors of scientific work.

Conclusion

We need a scientific community

Several years of work on the development of the Delphi Project have brought to the surface many of the challenges and pitfalls of clinical case research in homeopathy. The legal and ethical aspects have taken up the most time and energy, but it seems these can be overcome by a more formal description and organisation of the project. The variability in case reports and peer reviews however, are obstacles of another nature. It would appear that creating a coherent scientific community within homeopathy is a necessary precondition for successful clinical case research and this goes far beyond small-scale exchange projects.

As a first step towards this goal, in April 2003, a satellite congress to the bi-annual 'Improving Homeopathy' congress, organised by the Royal London Homeopathic Hospital, was dedicated to Delphi's clinical case research in homeopathy, and this has been reported.²

Lastly, the unpredictability of actual submissions seems to depend on motives that are not well understood. Specific research into this question may be of great value in advancing clinical case research.

Acknowledgements

I thank the Marion Meyenburg foundation for its generous support of this phase of the Delphi Project.

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