



THE JOANNA BRIGGS INSTITUTE

Future developments of systematic reviews and evidence based medicine

Jos Kleijnen

Oration
2007

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Jos Kleijnen, MD PhD

Contents

The Joanna Briggs Institute Oration 2007.....	5
2007 Orator	6
Future developments of systematic reviews and evidence based medicine	7
<i>Aetiology</i>	8
<i>Diagnosis</i>	8
<i>Prognosis</i>	10
<i>Preventative and therapeutic interventions</i>	11
<i>Decision making</i>	12
<i>Conclusions</i>	14

The Joanna Briggs Institute

Oration 2007

The Joanna Briggs Oration is a biennial event initiated by the Joanna Briggs Institute to serve as an occasion of celebration of the evidence-based health care movement, its accomplishments and to focus on visioning the future. This discourse brings together health professionals from a diverse range of backgrounds to celebrate achievements and anticipate the further evolution of evidence-based health care in the future.

2007 Orator

Jos Kleijnen is a physician (University of Maastricht, Netherlands), and is specialised as a clinical epidemiologist. Currently, he is director of an independent company, Kleijnen Systematic Reviews Ltd, which prepares systematic reviews and health technology assessments for various commissioners, and provides training courses in these areas. Previously, he was professor and director of the Centre for Reviews and Dissemination at the University of York; and director of the Dutch Cochrane Centre at the University of Amsterdam. His interests include: methodology of patient related research, health technology assessment, placebo effects, diagnostic and screening procedures, dissemination and implementation of research-based evidence, Evidence-based medicine, systematic reviews and the Cochrane Collaboration.

Future developments of systematic reviews and evidence based medicine

In this lecture I would like to address a number of issues which in my view are relevant or will become relevant in the next few years in the playing field of systematic reviews and evidence based medicine. A lot has happened since in 1991 Gordon Guyatt at McMaster University in Hamilton, Ontario, Canada coined the term “evidence based medicine.” At about the same time the term “systematic review” appeared, and in fact there was considerable overlap between the early champions of evidence based medicine and those of systematic reviews. The practice of evidence based medicine, or more broader, evidence based health care, depends on readily available information which has been critically appraised and summarised in an easily digestible way.

There have been a number of factors which have driven the steep rise of EBM and systematic reviews. One of the main factors was the emergence of information technology which has greatly facilitated access to information for health care professionals and perhaps more importantly, for the patients and the public. If doctors can't keep up to date with developments, patients will. Another main factor is the rising costs of healthcare, being felt in all countries, even the very richest. This has resulted in rationing of what is covered in health insurance or national health services. Very difficult and often unpopular choices have to be made everywhere, and a number of countries have established institutes that evaluate effects and cost-effectiveness of interventions. Cornerstones in such evaluations are systematic reviews and economic decision analytic models integrating costs and effects.

In epidemiology, medical research in patients is often divided into the areas of aetiology, diagnosis, prevention and therapy, and prognosis. I would like to address some recent developments and some future developments relevant to evidence based medicine and systematic reviews in each of these areas. I will end with some thoughts about making decisions in the era of EBM.

Aetiology

Although there have been early champions of clinical epidemiology such as Alvan Feinstein and David Sackett who focussed on patient care, a lot of what epidemiologists were investigating from the 1950s until very recently was in the domain of aetiology. Major new insights emerged about the aetiology of cardiovascular diseases and cancer, and in the areas of hygiene, diet and nutrition. However, the new concept of systematic reviews was not taken up as readily in aetiological epidemiology as it was in clinical epidemiology. Perhaps the complications of having to deal with observational study designs and problems with meta-analysis of such studies as opposed to randomised trials go some way to explaining this slow take-up.

However, in recent years this has been changing and in this context I would like to bring to your attention the efforts of the World Cancer Research Fund in trying to provide an overview about what is known about diet, nutrition, physical activity and the prevention of cancer. The WCRF have succeeded in bringing together some of the world-leading nutritional and cancer epidemiologists over a period of some 7 years and to develop a complete overview of all studies addressing the relationship between our dietary and physical activity habits and the occurrence of cancer. All of this by means of systematic reviews. At their website www.wcrf.org one can read: “..... in 2001, WCRF/ AICR set itself a new objective: to systematically review and assess the body of evidence on diet, physical activity and cancer and to publish a second expert report. This report is the largest study of its kind and its conclusions are as definitive as the available evidence allows. The WCRF network is committed to interpreting scientific evidence in this field and has set up a continuous review project to update the report on an ongoing basis.” I highly recommend you to visit their website and view and download the report.

Diagnosis

Arguably, diagnosis is a field doctors have even more uncertainties about than therapy. Tools to help clinicians interpret the findings of diagnostic test accuracy studies have been around since the 1980's, but one problem is that the accuracy of diagnosis of a certain state of health or disease is only one element of diagnostic research.

For example, diagnostic research may aim to assess whether a new test finds additional cases on top of those found by an existing test. A lot of testing is also done for monitoring purposes, be it for clinical or for legal reasons. Screening is a special case of using diagnostic tests. Furthermore, diagnostic research may aim to assess whether a new test should replace an existing one; whether a test can play a role as a triage instrument for possible further (invasive) testing; or what the most efficient order is in which multiple tests should be used. Finally tests may help to decide whether a treatment should be given, and if so to predict who will respond to treatment and who will get the adverse effects? The latter examples make the link with prognostic research, which essentially could be considered as diagnostic but linked to outcomes after follow-up rather than to a gold-standard.

Different diagnostic questions call for different study designs to address them. In addition, diagnosis by nature is a multivariable process, and this should be taken into account in diagnostic research. Evaluations of single tests are rarely clinically useful, unless meaningful sub-group analyses are possible. Diagnostic research is thus complicated and systematic reviews of diagnostic research are not for the fainthearted ones. In general, it is recommended to get a methodologist with experience in diagnostic research on board of any team trying to prepare a diagnostic systematic review. The Cochrane Collaboration is in the process of putting such support in place.

The Cochrane Diagnostic Test Accuracy Working Group was constituted to develop and implement reviews of diagnostic test accuracy within the Cochrane Collaboration. To be able to give authors and review groups all the support they may need, four regional Support Units are to be created. Two of these are already active: the UK Support Unit (UKSU) and the Continental Europe Support Unit (CESU). In October 2007, during the Colloquium in Sao Paulo, the implementation of systematic reviews of diagnostic test accuracy was officially launched. The new version of Review Manager, RevMan 5, will allow the preparation of reviews of diagnostic accuracy studies. Also, a Cochrane Handbook for diagnostic accuracy reviews is being developed. The Working Group members are doing their best to get all processes ready as soon as possible and will keep everyone up to date through the following website: <http://srdta.cochrane.org>

Diagnostic systematic reviews will remain in high demand and the Joanna Briggs Institute should consider how to address this demand.

Prognosis

I have already mentioned when talking about diagnosis that what doctors, patients and fourth-hurdle institutes such as the National Institute for Health and Clinical Excellence (NICE) in the UK ideally want to know is to predict who will respond to treatment and who will get the adverse effects? NICE recently approved two drugs for the National Health Service (NHS) under a deal with the drug company that the NHS will pay the drug bill for responders and the company pay for the patients who did not respond. In genetic research, investigators are aiming for similar goals.

However, it currently is extremely difficult to do meaningful subgroup analyses in systematic reviews; ideally one would need the individual patients' data in order to be able to do such analyses. In the longer run, we also need new guidance about subgroup analyses both in primary studies and in systematic reviews, because these will become increasingly important in answering the questions of the previous paragraph. Current guidance from methodologists and statisticians about subgroup analyses (which boils down to 'define them in advance and only do very few') is in my view similar to treating symptoms instead of the underlying disease.

Imagine the following ideal situation: we have resolved the issue of selective reporting of outcomes in randomised trials, for all trials there is a registry with their protocols, and it has become mandatory for authors to make the findings for all outcomes and all subgroups evaluated available in the public domain. Furthermore, we do not make our inferences based on an arbitrary p-value at the cut-off of $p < 0.05$ anymore. Instead, results are reported as point estimates with 95% confidence intervals; and readers of medical research have undergone a mandatory course about Bayesian inference. In this course they have learned expressing their prior belief about hypotheses to be investigated as a percentage with a "credibility interval" (similar to a confidence interval); they have also learned to change their prior belief to a posterior belief after having seen the study results for each subgroup. Silly examples of star signs significantly related to an outcome will be swiftly dealt with in such a ideal situation, because for most readers their prior belief will be so low that the findings of a single study will not change their posterior belief to a level that has any consequence.

With accumulating evidence, true effects will in due time lead to similar posterior beliefs amongst most health care professionals. We will also have got rid of the silly effect of current guidance about subgroup analyses which pretends that data are more true when a hypothesis has been defined in advance compared to a post-hoc hypothesis. The data are exactly the same in both situations!

Preventative and therapeutic interventions

Systematic reviews of preventative and therapeutic interventions have undergone a great development to the good side in the past 20 years. They are becoming higher quality pieces of research and recommendations from systematic reviews may also have had an impact on the quality of primary research.

However, developments will also in this area continue. One development will be that we will pay ever more attention to head-to-head comparisons of different treatment alternatives. Fourth-hurdle institutes such as NICE base their conclusions on such comparisons, whether a new drug is better than placebo when an effective other treatment is available is of limited importance. I predict that even the FDA in the USA in the near future will be permitted by Congress to demand head-to-head comparisons with existing effective treatments before licensing a new drug. It is unethical anyway to do a placebo-controlled trial when an effective treatment is available, isn't it?

Another development will be a more differentiated approach to the inclusion criteria concerning study design in systematic reviews. We will see fewer reviews which just include randomised trials; instead we will see separate inclusion criteria for addressing different outcomes. For example, in a systematic review of an analgesic, randomised (and double blinded) trials will be demanded to assess the effects on pain, and controlled observational studies will be demanded to address rare but important (adverse) effects. Qualitative studies might be included to clarify reasons for non-compliance.

Attention to adverse effects will become much more prominent. Different study designs may be needed for different questions: for the early recognition of rare but important adverse effects case reports will be the means of identification. Controlled observational studies such as case-control studies will confirm or refute suspicions raised by case-reports. Cohort studies and sometimes (meta-analyses of) randomised trials will allow a precise estimate of harm.

We will move further away from surrogate outcomes and go towards outcomes relevant to patients and reported by patients. Deveraux et al showed in the BMJ 2001, 24 November that patients and physicians may have very different perceptions about the importance of certain outcomes, as demonstrated by different judgements about serious bleedings as opposed to having a stroke. Again, forth-hurdle institutes are instrumental in setting the scene, they tend to insist on patient-relevant outcomes, and by doing that are most likely influencing the research stakeholders may planning to support their claims.

Decision making

"I am determined that no matter how much I trust my treating doctors, I want to be assured that the decisions we make together are based on as much evidence as is in existence at the time. I believe that is my fundamental right, and a right of others in a similar situation."

"The challenge I face in getting the evidence I need to make informed decisions is almost overwhelming"

"I also believe it is my right to determine the value that I place on different outcomes, to express my own treatment preferences (and have these taken into account), and to feel that my treating doctors are prepared to respect my experiences as a valid and important input when we come to make decisions"

Chris Silagy

'Introduction to the new edition: The Post-Cochrane agenda: Consumers and Evidence' (pp xix-xxx with quotes on pages xxvii) in Effectiveness and Efficiency: Random reflections on health services. The Rock Carling Fellowship 1971 by AL Cochrane. Royal Society of Medicine Press Ltd. London, 1999.

I find these quotes by Chris Silagy very powerful, and I thank one of the champions of consumer input into research, Gill Gyte, for drawing my attention to them.

Decision making in health care of course involves much more than evidence alone. Dave Sackett et al's 1996 definition of EBM published in the BMJ clearly reflects this: "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." Especially the word "judicious" is so important.

On the individual level priorities, needs, values and preferences come into play; on the organizational and national level, costs, resources, equity and innovation are other factors that may come into the decision making process on top of those of the individual level. Interplay between the patients and the health care professional is crucial and the professional should be conscious of the possibility that the patient's values and preferences may be very different from their own as shown by Deveraux et al. Muir Gray gave a nice example of the same phenomenon but then about disagreement between health care professionals and policy makers about breast cancer screening (BMJ 2004;329:988-9).

Barriers to getting the evidence needed for decision making are slowly being discovered and addressed, and information needed is increasingly becoming available. In fact the more broad area of knowledge transfer between basic and clinical research on one hand and between clinical research and practice on the other hand is being better recognized as crucially important and for example in the UK the The Medical Research Council (MRC) and the National Institute for Health Research (NIHR) have announced a new joint arrangement for clinical trials. The initiative forms a key part of the developing MRC-NIHR joint strategy for translational research. Its remit includes clinical trials and evaluative studies which add significantly to the understanding of biological or behavioural mechanisms and processes, explore new scientific or clinical principles, evaluate clinical efficacy of interventions where proof of concept in humans has already been achieved and the development or testing of new methodologies. The new strategy will ensure that promising technologies are carried from the efficacy and safety stage through to being assessed for clinical and cost-effectiveness to the NHS. The Cochrane Effective Practice and Organisation of Care group provides systematic reviews of the evidence concerning "getting evidence into practice".

Evidence is increasingly used and made a mandatory component of health care decision making around the world. In Germany, EBM has been written into the law, and in Brazil a law was passed (11.108/05) stipulating the right for women in labour to have an accompanying person with them, based on a systematic review!

Conclusions

Systematic reviews are currently being used in all areas of patients based research: aetiology, diagnosis, prevention and therapy, and prognosis.

Diagnostic research is complicated and when preparing systematic reviews of diagnostic research it is recommended to get help from a methodologist with experience in diagnostic research. Diagnosticsystematic reviews will be in high demand.

Prognostic research will focus on finding out who will respond to treatment and who will get the adverse effects. Guidance about subgroup analyses will need to be re-written.

Preventative and therapeutic reviews will focus more on head-to-head comparisons, address adverse effects and consider a range of study designs addressing different aspects of systematic reviews. Emphasis will shift further to patient relevant and patient reported outcomes.

Priorities, needs, values, preferences, costs, resources, equity and innovation are all factors that are part of decision making, in addition to the evidence of effects. Different parties may well have different views about a number of these factors.

Barriers to knowledge transfer are being investigated and EBM is becoming part of the law!



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