

Evidence-based medical practice: as viewed by a clinical epidemiologist

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Evidence-based medicine shifts the basis for clinical decision making from intuition and unsystematic clinical experience to the examination of evidence resulting from clinical research. Evidence-based medicine is the same as good clinical research. The selection of a proper study design for a specific study objective is the most important cornerstone of good clinical research. Evidence-based medicine places great importance on the design of a study, with optimum evidence being obtained from the randomised, controlled clinical trial. However, various study designs are equally important—if properly used—in the process of searching for solid and important evidence for use in clinical practice. There should be an emphasis on a quality improvement shift in research design from retrospective to prospective, cross-sectional to longitudinal, uncontrolled to controlled, and non-randomised to randomised. The reasons for using suboptimal study designs in clinical research are the lack of formal research training and the pressure to obtain academic output without being motivated. Research design is one of the most important aspects to study and practice, and there are four simple rules: (1) avoid retrospective studies; (2) focus on prospective studies; (3) use controls, randomisation, and blinding; and (4) always discuss the research design with an experienced researcher or statistician before commencing the study.

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What is evidence-based medicine?

Evidence-based medicine (EBM) is an emerging new paradigm for medical practice and undergraduate teaching. It shifts the basis for clinical decision making from intuition and unsystematic clinical experience to the examination of evidence from clinical research.¹ In recent years, the use of evidence-based decision making in health care has been gaining popularity. It requires that the results of primary research be compiled in a systematic manner and be made accessible to those involved in the decision-making process. With this approach, clinicians are aware of the evidence that supports their clinical practice and the strength of that evidence. Evidence-based health care promotes the collection, interpretation, and integration of valid,

relevant, patient-reported, clinician-observed, research-derived evidence.

Evidence-based medicine is here to stay

The main objective of EBM is to search for good evidence in the medical practice of patients. The first time I heard the phrase ‘evidence-based medicine’ was in 1989, when I was working as a visiting researcher at the University of Chapel Hill, North Carolina, the United States. Since then, EBM has become a subject of its own due to factors such as more emphasis on randomised controlled trials (RCTs) as representing the optimum evidence in medical practice,^{2,3} structured reviews that pool the results of several RCTs in a meta-analysis,^{4,5} the establishment of the Cochrane Collaboration, which emphasises structured reviews,⁵⁻⁹ the publication of various articles on EBM in journals of high repute such as the *Journal of the American Medical Association*^{1,10-23} and the worldwide acceptance of guidelines for clinical research—namely, the International Conference on Harmonization Good

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Clinical Practice (ICH GCP) Guideline,²⁴ which can also be found on the following website (<http://www.hku.hk/ctc/>).

In Hong Kong, there has also been some development in the EBM direction in recent years. For example, research-granting bodies require that much more detail be given in a study protocol to ensure support is granted to high-quality research in the first instance; the two medical faculties in Hong Kong have separately introduced various EBM-related courses, such as a course in EBM at The Chinese University of Hong Kong, and short courses and a Master of Medical Sciences degree in Clinical Trials Research Methodology at The University of Hong Kong²⁵; the Hospital Authority has introduced EBM in discussions of patient treatment from a cost-containment point of view; and the new undergraduate medical curriculum introduced this year by the Faculty of Medicine, The University of Hong Kong, is problem-oriented with a strong element of critical thinking, and reviews the current knowledge regarding disease patterns and disease management.²⁶

Evidence-based medicine is here to stay, including Hong Kong, and it will certainly play a major role both in clinical life, medical education, and clinical research.

Evidence-based medicine is the same as good clinical research

As the reader can tell from the various articles in this seminar series, EBM can have different meanings and is dependent on the personal experience and background of the writer. What does the phrase 'evidence-based medicine' mean to me? My personal view is based on 20 years' work experience in the areas of study design, study conduct, and the statistical analysis of clinical studies in various countries in Europe (the Nordic countries, the United Kingdom, and Germany), the Americas (the United States and Costa Rica), and in Asia (China, Hong Kong, and Pakistan). Much of my day-to-day work has also included reviewing submitted manuscripts and research applications, and the teaching and supervision of postgraduate students in clinical research. I have to say that too much clinical research produced today is of a relatively poor quality, since it is often based on retrospective patient data or case reports without the benefit of a prestudy-defined protocol; missing values and patient drop-out are common; the frequency of follow-up is related to disease grade and/or treatment response rather than all patients; the lack of concurrent controls is common; and the results are too often a consequence of data dred-

ging. This may sound a bit negative, but it is certainly grounded in fact. The following text is a description of possible and simple ways to improve clinical research.

Evidence-based medicine is about quality assurance

In most industrial productions there are various quality assurance programmes. To keep public confidence in a product high, the products must be of high quality at all times, equipment must be maintained, personnel have to be trained and re-trained, standard operating procedures have to be updated, and the products have to be routinely checked. Similarly, all new medical treatments—drugs, surgical procedures, devices, and prevention programmes—intended for use in the clinic have to be studied in a standardised manner. The results of such studies must be able to show evidence of both the efficacy and safety of the new treatment, and perhaps also data on health-related quality of life and cost-benefit aspects. Comparison should preferably be made in relation to the standard, or the current treatment of choice. Introducing a new treatment regimen without such a proper clinical study is no longer acceptable—testing a new treatment in a few patients without a predefined study protocol just to 'see what happens' is unethical, since the patients are put at risk, resources could be better used elsewhere, and the results are usually not acceptable for publication, and cannot serve as solid and reliable evidence on which to base medical practice. In a recent article in the *Lancet*, the common contention by clinicians that EBM is 'out-of-date' since medical practice changes rapidly was discussed.²⁷ The author concluded: 'Practice will become evidence only when clinicians refuse to experiment on their patients in an uncontrolled way, and when they understand that real progress in medical care will always be slow and more plodding than not if we are to honor the first law of medical practice, "first do no harm".'

The reason for undertaking good clinical research is that it represents an important dimension of patient care quality assurance.

What is good clinical research?

Firstly, good clinical research must be available to an academic audience, which means that only published studies can be seen as good research. Good clinical research has several elements, as shown in Box 1. The most important feature of good clinical research is the need for a well-defined study objective. The research question must be motivated from a clinical point of view, be able to be answered, and be based on the latest available information in the specific research

Box 1. Some important elements for performing good clinical research

- I Study objective—novel, important, and well defined
- II Study design—appropriate to the study objective
- III Data quality—standardised operating procedures, high compliance rates
- IV Statistical analysis—according to protocol, appropriate to the study objective
- V Scientific presentation of results—details of design, not only significant results
- VI Budget—include cost for statistical and editorial advice

area. Without a well-defined research question it is impossible to produce good clinical research—namely, research that can advance the management of patient care. Most clinicians are able to identify unknown patient-related research topics that could improve patient care significantly if the question were answered. Important research questions or study objectives could easily number in the hundreds or thousands if posed by a clinician specialised in a field. Hence, identifying the study objective is not really the critical issue in clinical research. Once the study objective has been defined, a suitable study design must be found and thereafter, high data quality needs to be ensured, proper statistical analysis done, the results presented scientifically, and appropriate financial resources need to be found (Box 1). Without a well-defined study design, high-quality clinical research cannot be achieved, regardless of data quality, statistical analysis, scientific presentation, and the financial resources involved.²⁸⁻³¹

The selection of a proper study design for a specific study objective is the most important cornerstone of good clinical research.

Evidence-based medicine is about study design

With this as background, I would like to focus on the importance of selecting the most suitable study design to yield the answer to a particular clinical research question. Evidence-based medicine usually ranks the evidence according to the study design—an evidence grading of I to III (Box 2).²⁻³ The ‘best’ evidence—grade I—is generally accepted to be obtained from the RCT, whereby a new treatment (or prevention programme) is compared with a standard or placebo treatment. Randomisation into treatment is the optimum way to avoid selection bias, which occurs when the two study groups are different at baseline in important measures, for instance, in age or disease stage. One source of variation that may introduce

Box 2. Evidence grading of clinical research in order of reliability²⁻³

- I Randomised, controlled clinical trials
- II Non-randomised clinical studies
- III Clinical experience

selection bias into the study results arises when, for some reason, one patient category is selected for one particular treatment. When the doctor is allowed to select the treatment, the treatment effect can be exaggerated by up to 40% in favour of the new drug because patients with the best prognosis are commonly, if subconsciously, selected for the new treatment.³ Another way to control variation or bias in the evaluation of treatment effects is to make the study blinded—that is, to withhold information on which treatment is being administered to which patient. When the doctor and the patient know which treatment has been selected, knowledge of the treatment influences the evaluation of the outcome measure of the study and the treatment effect may be exaggerated by up to 17% in favour of the new treatment.³ In addition, studies using historical controls have claimed a 59% better response than those using randomised controls.³⁰ For these reasons, the Cochrane Collaboration and meta-analysis are almost solely based on results obtained from randomised study trials.⁵⁻⁹

Evidence-based medicine rates as primary the evidence of a study and the optimum evidence is provided by the randomised, controlled clinical trial.

The practice of randomised study design

The practice of the randomised, controlled study design is not frequent in Hong Kong; 3% of the medical academic output of any type included in *Medline* in the years 1987 to 1996 used the randomised study design, with no change in this figure over the decade of study³²; local non-indexed journals, such as the *Hong Kong Medical Journal (HKMJ)*, did not include any publication based on an RCT between early 1995 to September 1997. It should be mentioned, however, that other countries, although with some exceptions, are not doing any better in this respect (unpublished observation). Similarly, in most western countries, the randomised study design represents about 3% of the *Medline*-indexed publications. There is, however, a clear trend for some medical journals with a high impact factor to have increased the number of publications based on RCTs significantly over recent years.³¹

In many areas of medicine, more emphasis is being given to the use of proper research designs. This has

been described in, for instance, neonatology³ and surgery, but the change in this direction has not yet really happened. The following example is taken from surgery, since it may be seen as an area with less potential for the randomised, controlled study design: Solomon and colleagues in the Department of Surgery, University of Toronto, in Canada, have published three studies on RCTs in surgery.³³⁻³⁵ They found that there has been no overall increase in the proportion of good clinical trial designs, as published in a selection of journals reviewed between 1980 and 1990. Only 6% of all published surgical studies were RCTs. However, even in the ideal situation, the authors consider that the RCT can be used to evaluate only 40% of treatment questions involving surgical procedures.

Improvements can be made to research design so that better evidence can be provided for patient care.

Various study designs are equally important

Personally, I object to the proposal that good clinical research can only be obtained from RCTs, although we should always use this research design, if possible. It is only in the final stages of development of a new treatment or intervention process that we are able to use the randomised type of study design to confirm the efficacy and/or safety of a procedure. Extensive exploratory research has to be conducted before confirmatory research can be done, and exploratory studies provide very important information that can direct changes in medical practice.

Various study designs are equally important—if properly used—in helping to find solid and important evidence on which to base clinical practice.

The important study designs

There are various ways to describe a study design, which include: (1) cross-sectional or longitudinal; (2) observational or experimental; (3) retrospective or prospective; and (4) population- or hospital-based. A more practical way is to describe the most common types of study used in medical research. We start to define the design after the purpose; is it an observational or an experimental study (Table 1)? Observational studies can describe various important aspects about a certain disease such as the prevalence, incidence, natural history, and potential risk factors associated with the disease, or they can be used to evaluate diagnostic tools or to develop clinical reference values. But they can never provide evidence for medical practice in terms of treatment choice for an individual patient. For this, we need experimental studies of a prevention or treatment type. Not all

Table 1. Common study designs used in clinical research

Design type	Study objective
<i>Observational</i>	
(1) Case report	Description of an unusual case, or case series
(2) Cross-sectional	Prevalence Reference values Diagnostic test
(3) Case-control	Risk factor association Protective factor association Effectiveness of screening
(4) Prospective	Prevalence or incidence Reference values Prognostic or diagnostic tests Natural history of disease Risk factor association
<i>Experimental</i>	
(5) Retrospective	Exploratory
(6) Non-randomised	Exploratory
(7) Randomised	Confirmatory and exploratory

experimental studies are confirmatory, providing information about the efficacy of a certain treatment; many experimental studies are exploratory in nature. Most RCTs have a primary research question followed by various secondary exploratory research questions, which are not defined in detail in the pre-set study protocol.³⁶ Strictly speaking, any result obtained without randomisation to treatment, without the use of concurrent controls, and that was not intended to be tested prior to the study cannot be seen as solid evidence in medical practice. Such results should be regarded as tentative information only, to be confirmed in a later study.

Result interpretation should only be done with due consideration of the study design.

A focus on locally published clinical research

The medical academic output in Hong Kong is relatively high³²; 600 to 700 publications were found for each year in *Medline* during the past 5 years with 'Hong Kong' in the correspondence address field. Many of these publications appear in well-known international journals, sometimes with a very high impact factor. However, there is no local Hong Kong journal that has as yet been included in *Index Medicus*, unlike journals from Taiwan, Singapore, and China. As a consequence, most important research done in Hong Kong is published in international journals, rather than in local medical journals.

Hence, it is interesting to find out what kind of studies are published locally, and what their evidence

Table 2. Study designs used in all original articles and case reports published in the *Hong Kong Medical Journal* between 1995 and 1997, and the *Lancet* in 1997*

Design type	<i>Hong Kong Medical Journal</i> 1995-1997 No (%)	<i>Lancet</i> 1997 No (%)
<i>Observational studies</i>		
(1) Case report	32	51
(2) Cross-sectional	21 (40)	42 (23)
(3) Case-control	2 (4)	21 (12)
(4) Prospective	5 (10)	36 (20)
Subtotal	28 (54)	99 (55)
<i>Experimental studies</i>		
(5) Retrospective	19 (36)	3 (2)
(6) Non-randomised	4 (8)	8 (4)
(7) Randomised	1 (2)	70 (39)
Subtotal	24 (46)	81 (45)
Total	52	180

* The case reports were not included in computing the percentages

ratings are. For this purpose, original articles in the last 3 years' issues of the *HKMJ* were reviewed in terms of the type of study design used. Fifty-two such articles were studied and the results are listed in the Table 2. For comparison, the design of all 180 original articles published in the *Lancet* in 1997 were reviewed in the same manner and the results are also shown in the Table. Only the number of case reports is shown; these were not included in the computation of percentages. Usually, only one case report is included in each *Lancet* issue, while the *HKMJ* has on average, three such articles in each issue. Retrospective studies of hospital records were all labelled as 'Experimental studies: 5. retrospective' in the Table even though some were not really experimental by definition, but were of the standard patient management type.

The percentages of observational (54% for the *HKMJ* and 55% for the *Lancet*) versus experimental (46% and 45%) studies published were similar for the two journals. The *Lancet* included, however, more case-control studies (12% versus 4%) and prospective studies (20% versus 10%) than did the *HKMJ*, under the observational category. The *HKMJ* observational studies were mostly cross-sectional in nature and hospital-based, and did not often try to identify risk factors or predictive factors, produce local clinical reference values, or describe the natural history of a certain disease. In the *Lancet*, the experimental studies were largely dominated by results from RCTs—39% versus 2% in the *HKMJ*. On the other hand, most of the experimental studies published in the *HKMJ* were based on retrospective data—36% of the total, or 19

of 24 experimental studies. Those studies were usually based on hospital records—that is, without randomisation to treatment, no blinding, no concurrent controls, and without any pre-set study protocol.

It is not intended here to compare the scientific standard of the *HKMJ* with one of the top international medical journals. We cannot blame a local, non-indexed, medical journal for publishing articles with relatively poor study design quality, since it can only publish what is offered from the scientific community. Consequently, the clinical research published locally can only partly help local doctors to identify good and solid evidence on which to direct their medical care of patients. In addition, considerable effort and resources are spent on studies that have suboptimal study designs. *An effort should be made to improve the quality of research done, by using designs that are prospective rather than retrospective, longitudinal rather than cross-sectional, controlled rather than uncontrolled, and randomised rather than non-randomised.*

Why do we use suboptimal research designs?

There are two reasons why we use suboptimal study designs in clinical research—lack of training and lack of motivation. Firstly, most doctors lack formal training in clinical research methodology, such as study design, sample size calculation, biostatistics, results presentation, results interpretation, and scientific writing. We do not expect to be good clinicians without formal training and practice, and likewise, we should not expect to produce good research without appropriate

training and guidance in the art of clinical research.

Secondly, many clinicians lack motivation; they are pressured to do research but have no real desire of their own to be involved in research. There are various reasons why those who are less motivated have to be involved in research; active research improves promotion prospects and senior doctors require some research output from visiting fellows or from more junior staff members. In this situation, the aim is reduced to one of producing some publishable research results in a short time without any major effort and financial support. One easy way to get data is to simply retrieve some patient files and review the first 20 to 40 subjects identified; whatever the results are, the objective is to get them published. Such research is publication-driven rather than patient improvement-oriented, and it will seldom yield results that can be regarded as solid evidence.

The reasons for using suboptimal study designs in clinical research are both the lack of formal research training and the pressure to obtain academic output without personal motivation.

Two illustrations of evidence bias

A study we conducted based on retrospective hospital data, found that 65% of babies born small for gestational age increased their body size to that of healthy babies during the first year of life³⁷; this figure increased to 90% in a prospective study that looked at babies born a few years later in the same hospital.³⁸ The latter figure is very much in line with the results of other studies. The reason for the difference in the results of the two studies was the presence of a drop-out bias in the earlier study: infants with no health problems and/or with normal growth rates were not followed for more than a few weeks or months postnatally, so long-term data on the healthier babies were missing.

Children who are short in childhood may benefit from growth hormone treatment, but many of these children have been given such treatment without the use of a proper study design (eg no inclusion or exclusion criteria, no pre-set study protocol, no controls, etc) Some publications based on such series have shown a long-term treatment benefit of 3 to 6 cm in height. However, the drop-out rate is not always described and is known to be quite high. One reason for stopping the treatment is the lack of a good treatment response, since growth hormone is an expensive product. The children who remain for analysis are thus the responders, which subsequently introduces a performance bias into the data.

Selection and performance bias can only be avoided by using a good research design—namely, prospective studies of various types.

Simple ways to improve clinical research design

The various parties involved in producing and publishing medical research, such as the investigator, the sponsor, the research-funding body, the regulatory authority, and the editorial board must take responsibility for improving clinical research practice, as we have discussed elsewhere.³⁹ To avoid the common mistakes made in research, we need to introduce formal training in clinical research at various levels.^{25,39-43}

Study design is one of the most important factors in clinical research; four simple rules to follow are: (1) avoid retrospective studies, except for well-designed case-control studies; (2) focus on prospective studies with a well-defined study protocol, since they can provide the best evidence for medical practice (Table 1); (3) consider the use of controls, randomisation, and blinding; and (4) discuss the research design with an experienced researcher or statistician.

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