Clinical Research Practice

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Evidence-based medicine (EBM) is emerging as a new paradigm for medical practice and undergraduate teaching. The widespread acceptance of this concept has important implications for clinical practice and research. Clinical decisions should now be based on sound research-based rationale rather than intuition or anecdotal evidence.[1-3] While EBM has become increasingly popular, it can only be achieved if research results are compiled in a systematic manner and made widely accessible. In a short commentary Wagner[4] concluded that 'Practice will become evidence-based 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 honour the first law of medical practice; "first do no harm".' Evidence-based health care promotes the collection, interpretation and integration of valid, relevant patient-reported, clinician-observed, research-derived evidence. Randomised controlled trials provide the most valid basis for comparison of interventions in health care and offer the most reliable information for clinical practice.[5-7]

High quality clinical research is a prerequisite of EBM. High standard research is the responsibility not only of the investigator but also of the regulatory authorities, funding organisations, universities/hospitals and the editorial boards of scientific journals. Unfortunately, clinical research studies can be based on flawed methodology. Common problems in study design include lack of randomisation, lack of a control group, and small sample size.[8,9]

Poorly designed studies continue to be published. One reason is that the urge to publish is often career-driven. A second reason is that statistically significant results are more likely to be published than non-significant results, hence data is manipulated to produce the desired results. Can we change this behaviour or practice? The answer is "yes". Several important steps have already been taken to improve the quality of clinical research, but more can be done.

RESPONSIBILITY OF THE REGULATORY AUTHORITIES

The drug regulatory authorities, in conjuction with the pharmaceutical industry, notably the International Federation of Pharmaceutical Manufacturers Association (IFPMA), have made a major contribution to improving clinical research.

The International Conference on Harmonisation (ICH) held in 1989, brought together the regulatory authorities of Europe, Japan, and the United States, and the pharmaceutical industry to standardise requirements for registering new medicinal products. The primary aim of the ICH is to expedite the global development and availability of new medicines without compromising patients' rights and confidentiality, quality, safety and efficacy. After several years and several drafts, the Inter-

national Conference on Harmonisation's Good Clinical Practice (ICH GCP) Guidelines were published in 1996.[10]

The guidelines primarily target large international and multicentre clinical trials, but apply equally to smaller trials. If the principles of the ICH GCP Guidelines were more broadly adopted, great improvements in clinical research might be attained.

The basic principles of the ICH GCP Guidelines are well defined, logical and irrefutable. Trials should be designed to provide reliable and useful information on the treatment in question. A poorly designed trial usually fails to achieve an advance in medical knowledge, and is therefore unethical and wasteful.

APPLYING THE ICH GCP GUIDELINES

One point that has not been specifically addressed in the ICH GCP Guidelines is the observation that the tolerance and efficacy of a drug is affected by the ethnicity of the patient. Since 1990, many studies have highlighted the differences in drug responses between Asians and Caucasians. Very little clinical trial data can be extrapolated from one ethnic group to another.[11,12] Local or at least regional data on specific ethnic groups must be sought. Debate should be encouraged on this subject and future clinical trials should be broadened to consider gender and age in addition to ethnicity. The ICH GCP working group is currently considering such a proposal.

The Role of Editorial Boards

International journals such as the *Lancet, New England Journal of Medicine, British Medical Journal, and Journal of the American Medical Association* have joined the crusade for good clinical research. The *Lancet* will only accept papers that comply with international standards for the conduct and reporting of clinical trials.[13] Study authors therefore need to be fully conversant with the ICH GCP Guidelines when planning their methodology. Unfortunately, not all journals are as strict.

One criticism is that studies are not accepted for publication if their results are not statistically significant. All-out attempts are then made by the authors to achieve statistical significance by analysing their data in as many ways as possible. In extreme cases, the number of statistical tests performed can exceed the number of subjects tested.

The need for a control group has also been the subject of ethical debate. It has been argued that it is unethical to randomise patients to nontreatment or placebo groups, and so deprive them of a potentially beneficial treatment. However, it may be just as unethical to promote a certain treatment without having solid evidence for its validity. The results from non-randomised studies can provide important information for future research, but they should not be allowed to dictate medical practice, especially if the study was originally designed for another purpose. Editorial boards should be responsible for preventing over-generalisation and ensuring that results of non-randomised clinical studies are viewed in context.

Systematic reviews of published studies should provide the evidence for the 'best medical practice'. Evidently, there is also a need for physicians to improve their skills in reading articles.[14]

Responsibility of Investigators

The principal investigator bears overall responsibility for the clinical trial. Ideally, the study should conform to the standards set by the ICH GCP Guidelines.

A recent study in Hong Kong showed that many academics and pharmaceutical company personnel were not conversant with the guidelines.[15] A questionnaire completed by 273 clinical research personnel working at hospitals or in pharmaceutical companies between May and August 1996, revealed that the practical concepts of GCP Guidelines were not widely publicised. Poorly educated and unskilled personnel may com-

promise the standard of clinical research, so formal and informal clinical trials training programmes must be developed. It is clear from the study that experienced and inexperienced staff need this training. It should therefore be offered to undergraduates and experienced clinicians alike.

To ensure high quality ethical medical research, all staff involved in human research should be familiar with the ICH GCP Guidelines.

An Example of not Complying With the ICH GCP Guidelines

In the field of paediatric endocrinology recent reports have voiced concern over the use of growth hormone (GH) promoting treatments, not only for GH deficient children but also for other conditions such as Turner's syndrome, chronic renal failure, small for gestational age children and short normal children. Several studies involved non-randomised trials with effect of treatment assessed by comparison with either concurrent controls, historical controls, or left uncontrolled. A lack of randomisation of subjects into active treatment or placebo groups ensured results would be inconclusive. Another potential source of bias was that the number of subjects who dropped-out was unusually high in these studies and their characteristics were not reported. It is a matter of great concern that these patients might have been "the non-responder" group. These studies were usually 'long-term' (over 5 to 10 years) continuing until final heights had been reached with daily GH injections and consequently very costly. It is clear that many of these studies do not comply with the ICH GCP Guidelines. Why are we treating patients for years at an alarmingly high cost without any opportunity to evaluate any potential benefits? Is it because we have not been trained in clinical trials research methodology including the principles of GCP, or are there other reasons?

Responsibilities of Funding Organisations

Pharmaceutical companies are now required to ensure studies they fund conform to the GCP Guidelines. This means research will be of good quality and has the added advantage that companies may be assured of the validity of the results. Hospitals, and other non profit-making organisations now also want a similar kind of assurance before they fund clinical research. In some cases, funding is not made available until approval of the study protocol has been given by an independent ethics committee. Some organisations also require approval of the study design, which should be based on the GCP Guidelines, by a research committee. To ensure quality assurance, studies should be continually monitored. This practice is usually confined to pharmaceutical company-sponsored studies.

Responsibilities of Universities and Hospitals

One feature of the ICH Guidelines that should have a significant impact is the requirement for investigators to obtain a statement

GCP Guidelines Training at the University of Hong Kong

The Clinical Trials Centre at the University of Hong Kong is a new venture that aims to co-ordinate and support clinical trials, education and training in Hong Kong and throughout the region. The Centre runs sixteen courses on various aspects of clinical trials research methodology.

The importance of training staff who conduct clinical trials has long been recognised.[16-19] The ICH Guidelines state: each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).[10] Because more pharmaceutical companies are entering the Asian market, more Asian countries are becoming aware of international standards of drug regulation. Consequently, there is a need to educate Asian medical staff in all aspects of clinical research methodology and good clinical practice. To address the long-term need for qualified personnel, a Master of Medical Sciences (M Med Sc) degree in clinical research has been developed at the University of Hong Kong.[20]

from an ethics committee that the trial "is organised and operates according to the GCP Guidelines and the applicable laws and regulations". These recommend that the committees include:

"(a) at least five members, (b) at least one member whose primary area of interest is in a nonscientific area, and (c) at least one member who is independent of the institution/trial site."

The committee "should perform its functions according to written operating procedures" and "should maintain written records of its activities and minutes of its meetings". These records should be retained for at least three years after completion of the trial. A principal investigator wishing to conduct a clinical trial which follows the ICH GCP Guidelines — a prerequisite for international publication and recognition—should first check that the local ethics committee also recognises the guidelines. An institution should also always insist that all human studies performed under its name have ethical clearance. Ethics committees should not only concern themselves with the ethical aspects of a protocol, but also its scientific value, the study design and resources allocation. Institutions do not currently monitor studies carried out on their premises: inspection of the studies every year should provide quality assurance.

CONCLUSION

The practice of EBM requires the availability of sound and unequivocal scientific data which can only be obtained from well-planned, carefully-designed, prospective, randomised, controlled clinical studies. The design of these studies will benefit from reference to the principles of good clinical practice as outlined by the International Conference on Harmonisation in 1996.[10]

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The ICH GCP Guidelines are available from the ICH Secretariat, IFPMA, Geneva, Switzerland and the University of Hong Kong Clinical Trials Centre home-page (http://www.hku.hk/ctc).