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

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In this era of information technology, clinicians need to understand how to conduct ethical and effective clinical research. The principles of 'good clinical practice' have been established to prevent mistakes and malpractice, and to protect research subjects. A researcher must carefully design the study and perform a thorough review of the literature. A detailed protocol that has been approved by the institution's Ethics Committee must be constructed before commencement of the study and followed accordingly. Comparable control group(s), recruited in a double-blind fashion, ensure that the effects observed are specific to the intervention itself. While a retrospective data review is sometimes useful, only prospective studies provide solid evidence. Outcome parameters must be defined that are clinically appropriate and measurable. Subjects should only be recruited with consent and in a randomised fashion. Elimination of inter- and intra-observer errors can be achieved by appointing an assessor (or team) and by training personnel. Proper documentation of all the events and outcome parameters is of paramount importance and is a requirement for good clinical practice. Data analysis should be done by a qualified and experienced biostatistician and the personnel involved in the study must be fully aware of their moral, legal, and scientific responsibilities and be able to work with each other.

HKMJ 1998;4:175-82

Key words: Clinical trials; Ethics/medical; Evidence-based medicine; Practice guidelines

Introduction

One definition of the practice of evidence-based medicine (EBM) has described it as "the practice of medicine which eliminates the use of expensive, ineffective or dangerous decision making."[1] This means that the clinician has to critically appraise and apply current evidence in clinical practice.[2] The paradigm of decision making under EBM ensures that effective care of the individual occurs. There is no doubt that EBM is essential in this era of information technology. Historically, the development of EBM has paralleled the sophistication of clinical trials methodologies. Many would agree that advances in clinical trials methods lead to the development of the concept of evidence-based medical practice.[3] The development of progressively more rigorous clinical trial methods has generated more controlled and better quality data on which to base the clinical management of patients. However, it is also increasingly more evident that the daily practice of medicine is not always in line with the results of contemporary quality clinical studies.

There are usually two ways for clinicians to obtain properly controlled clinical data—from clinical trials and surveillance studies. The importance of clinical trials as regards the development of medicine cannot be stressed too strongly.[1-6] This is reflected by the many articles in clinical journals that are related to clinical trials. For example in 1997, about 40% of the original articles published in the *Lancet* described results of clinical trials. Investigators used to perform clinical trials in their own way because there were no 'guidelines'. Whereas the purists wish to obtain absolute evidence from human experimentation, the moralists wish to perform no trials at all as all patients should receive the best treatment.[7] Both of these extreme views are illogical and against EBM principles. A sensible compromise is to obtain the best possible evidence within ethical constraints. Many reader-friendly books and articles discuss methods by which medical and scientific information can be found and then translated into everyday clinical practice.[3-6] Unfortunately, the methods needed to extract solid and ethical evidence are usually only described in statistically-oriented textbooks that are often inaccessible and incompre-

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hensible to many busy clinicians.[8-11] This short article has been written with the aim of bridging this gap for general readers. The techniques and theories on performing surveillance studies are largely epidemiological and will not be described here.

Why do clinical trials?

A clinical trial is a study of the action of a therapeutic or diagnostic intervention with a drug, device, or health care product in human subjects. As the untreated state of most diseases displays some longitudinal variation, the mere observation of a 'clinical improvement' does not necessarily imply a beneficial effect due to a drug or treatment protocol. Several confounding factors are present, many of which are unknown, which could affect the results of a trial. The different stages in the development of a drug and the associated clinical trials are shown in Box 1.

The aims of a therapeutic trial must be clearly defined and generally encompass one or more of the following: whether or not a treatment is effective; the efficacy of a treatment (with or without comparison with other modes of therapy); the identification of which patient subgroup is likely to respond; administration details such as the optimum route and dosage; and monitoring of any adverse reaction.

Good clinical practice and the International Conference on Harmonization guidelines

The gold standard clinical study, particularly therapeutic or interventional, is undoubtedly the 'prospective, randomised, double-blind and placebo-controlled study with data monitoring and preceding sample size calculation'. All good clinical studies should comply with the principles of good clinical practice (GCP) that were published in 1996 in the International Conference on Harmonization (ICH) technical requirements for the registration of new drugs. Unless these guidelines are observed, the results of a drug trial could be viewed as 'invalid' as far as registration of a new drug is concerned.[8]

The GCP guidelines are a set of management procedures designed to prevent mistakes and malpractice and to protect research subjects; GCP sets the standards for the ethical evaluation of clinical research with the aim of securing the safety and rights of trial participants. In addition, GCP outlines the activities, from the planning to concluding stages, of the investigators and/or sponsor, and monitors the trial to ensure that the data and the reported results are credible, accurate, and useful.[12-14]

The ICH technical requirement for the registration of pharmaceuticals for human use has produced a set of guidelines on GCP. The guidelines have taken into consideration the usual practices in the United States, the European Union, Japan, and Canada, and must be followed whenever possible. Although the guidelines were well publicised,[12-14] a recent local study has conclusively shown a lack of such knowledge among clinicians and pharmaceutical personnel.[15]

Study design

Poor study design leads to the generation of poor-quality data, which means that trial patients undergo risks unnecessarily, resources are spent unjustifiably, and investigators' energy and time are wasted. All clinical trials must have a fairly lengthy written protocol and this should remain as the 'map' throughout the study. The design of a study should contain details of the aims, the rationale for the design, the inclusion and exclusion criteria used for patient recruitment, the

Box 1. The various stages of clinical trials

Phase	Features
I	Clinical pharmacology (20-50 subjects) Usually healthy or occasionally patient volunteers Pharmacokinetic determination (absorption, distribution, metabolism, excretion, etc) Pharmacodynamics (biological effects) investigated Safety profiles
II	Clinical investigation (50-300 subjects) Targeted patient group Pharmacokinetics, pharmacodynamics, and dose-finding investigated
III	Therapeutic trials (>250 subjects) Efficacy and safety studies with or without comparison with established treatment
IV	Postmarketing surveillance (>2000 subjects) Long-term safety and efficacy surveillance Efficacy comparison studies

withdrawal procedures for patients, the statistical basis of the study, and give details about the investigator.[16]

The background to a study

Consultation with leading experts (eg through collaboration or attendance at international scientific meetings) and a critical review of the literature may help identify 'gaps' in the current knowledge.[3-6] All researchers are human and have limited expertise, time, resources, and energy. The design of a prospective study should therefore be sensibly restricted to address 'gaps' in the knowledge that interest the researcher. In this way, the most scientifically and clinically worthy results can be expected, which will be collected enthusiastically by the researcher.

Need for a control group

As disease activity fluctuates in most diseases, whether or not the patient is receiving efficacious treatment, overt improvement or deterioration after the initiation of a new treatment in a clinical trial does not always indicate efficacy or a deleterious effects.[17] The temptation to give the 'new' treatment to all the patients, thereby 'saving' time, energy, and resources must be resisted. The need for a comparable and parallel control group is present in most, if not all, clinical trials.[17] This will reassure the investigators that the results (benefits or otherwise) observed in the treated patients are more likely to be specifically related to the treatment itself rather than a mere reflection of changes in the environment, diagnostic standards, concurrent diseases, or other unexpected confounding factors, including the formidable placebo effect.[18] Recruitment of a comparable control group is best done by the randomisation process in a double-blind study.

The need for prospective data

The use of historical information obtained for the same or other patients to provide control data (ie the use of historical controls) is a common practice that can lead to the generation of poor quality conclusions.[19] Data from the same patient group may vary tremendously over time, even in those with chronic diseases. The use of a non-concurrent control group may therefore introduce a huge bias, due to a difference in environmental, non-medicinal, or various other variables that a researcher cannot account for. It is therefore best to start with prospective studies when the data can be collected in parallel from the control and test groups by the researcher.

Construction of a protocol

A protocol should be written to satisfy the following requirements[9,16]: the study must be ethical and provide for the protection of the rights of the subjects; the study parameters should be sufficiently sensitive; adequate measures must be included to determine the safety of the drug; the study design must be scientifically sound and acceptable to the investigators; the protocol must meet all legal and regulatory requirements; and the number of patients involved in the study must be stated and justified. The writing of a protocol is complex and beyond the scope of this short article. However, the components of a standard protocol are outlined in Box 2.

Definition of outcome parameters

The literature review and expert consultation should yield some information on the gaps in the literature and also likely parameters that are meaningful both clinically and scientifically. These parameters must also be sufficiently sensitive (ie measurable) and their

Box 2. Components of a standard protocol

(1) Standard cover page: title, date, protocol number, test medicine, form, regulatory status, name, address, telephone numbers of the sponsor
(2) Background: brief description of the scientific and clinical data
(3) Objectives of the study: definition of the primary endpoint
(4) Recruitment criteria
(5) Study design: eg double-blind, placebo-controlled, randomised
(6) Drug treatment plans: form, strength, timing, duration, labelling and storage conditions, etc
(7) Parameters assessed: primary and secondary efficacy measurements
(8) Flow chart of the study logistics
(9) Adverse drug events: define 'serious' and report out-of-hours problems
(10) Name of the Ethics Committee
(11) Description of the consent process with reference made to the Helsinki Declaration, 1964
(12) Statistical information: sample size, analysis plan, etc
(13) Data management plans: especially if a contract research organisation is engaged
(14) Auditing procedures: state frequency and methods
(15) Declaration of insurance
(16) Criteria for termination of study: including completion of recruitment, reasons for pre-mature termination, etc
(17) Appendices usually include: the consent form, references to investigative procedures, and a copy of the Helsinki Declaration, etc

measurement feasible within the capability of the investigators. Definitions of the primary and secondary outcome measures must be made to help focus the research. Indiscriminate collection of numerous parameters, irrespective of clinical or scientific justification, is sometimes done just to ensure that a 'positive' result is generated by a study. This is both unethical and scientifically unsound, and predisposes to the 'discovery' and subsequent reporting of a 'chance finding'.[20,21]

Elimination of data bias

Bias can be introduced at various stages of a study that will compromise the analysis and interpretation of data. The most important feature in the design of a clinical trial is the elimination of any possible known bias. Bias can occur in many ways at various stages.[8-11] The literature review process has an intrinsic publication bias as positive results are likely to be published in more prestigious journals and therefore be read by fellow researchers. This might artificially enhance the effects of a certain treatment as any failures are less frequently reported or only reported in less prestigious journals. The selection of patients is also important as a selection bias will result in invalid comparisons being made between the control and test groups. Investigators could also bias a study through improper execution of the experimental procedures. Measurement of outcome can also be biased as some investigators tend to ignore the unwelcome results, particularly minor to moderate adverse reactions to a test drug. Data interpretation can also be severely biased if the researcher is keen to produce 'positive' results that will help achieve publication of the work in journals.

A prospective, double-blind study whereby patients are randomly recruited using the same stringent inclusion and exclusion criteria has the greatest probability of reducing bias in recruitment, execution of procedures, and outcome assessment. Asking the statistician to perform analysis without knowing the treatment received in the trial also eliminates some bias, although the principal investigator bears the final responsibility of interpreting the results fairly and correctly in a logical and scientific manner.[8-11]

Recruitment of subjects

The criteria used for subject recruitment must be defined before the study commences and then followed rigidly. Any subsequent alteration must be resisted and must be agreed on by the principal investigator, sponsor, and ethics committee. Inclusion criteria generally include the age range, gender, disease diagnostic criteria, and disease severity markers for the prospective patients. The severity markers generally also constitute the parameters to be measured in the study and it is of utmost importance to define these quantitatively wherever possible. Exclusion criteria must also be carefully laid down. These generally include known adverse reaction(s) to the test treatment, consideration of child-bearing potential for most drugs with the remotest teratogenic potentials, concomitant conditions, and disease-specific criteria.[8-11, 22-24]

The randomised recruitment of patients, sometimes regarded as inconvenient by many investigators, is one of the most important ways of eliminating selection bias, particularly when combined with a double-blind design.[25] The randomisation process can be simple, block, or systematic block in design. Simple randomisation entails the assignment of treatment (equivalent to tossing a coin) and is the most elementary and commonly practised method. Unequal allocation can result, however, particularly if the sample size is small, making subsequent analysis very difficult. Block randomisation using a fixed treatment sequence (eg ABAABBBA for a 'block' of eight patients receiving treatment arms A or B) is more advanced and convenient enough for mostly clinical research practice. Systematic block randomisation assigns a patient to a treatment based on a random order in the first block, which is then repeated in all subsequent blocks.[16,25]

Written informed consent, in the subject's native language, must be obtained in all clinical therapeutic studies.[26] The first portion of the consent form generally describes the study and nature of the subject's involvement while the second part is where the subject should sign. The principal investigator and a witness should also sign the form stating that the investigator has explained in full the nature of the study to the subject. As the first part of the study describes the aims, stages, procedures involved, and possible adverse reactions from the test treatment, it is standard practice in the West to issue a copy for the patient to keep, although this practice is not yet common locally.

Elimination of intra- and inter-observer errors

Biological data are usually not perfect and errors can arise in the following situations: by sampling the wrong group (ie one atypical of the entire population); through systematic errors, introduced by faulty measurements made by personnel or due to defective equipment that has not been calibrated; because the distribution of data is asymmetrical or skewed; and by observer

variation—intra- and inter-observer error can be reduced by using the same assessor and equipment throughout the study.

Intra-observer variation can be lowered by improving motivation, training staff, eliminating personal biased and pragmatic views, and numerical preferences (eg a dislike of the number '4').[27,28] Inter-observer variation can be problematic, particularly in multicentre large-scale studies when the same assessor cannot be deployed to assess the entire patient cohort. For instance, the assessment of test and control groups of patients in a therapeutic study by different investigators could potentially introduce fundamental inter-observer errors into a study that will completely invalidate the data. Reduction of inter-observer errors can be achieved by appointing an assessment panel or reference laboratory, or by appointing a well-trained and qualified, enthusiastic assessor to the research team who makes all assessments. Multicentre studies need more logistic planning for this purpose and usually require attendance at qualifying training courses by the prospective assessors.[27,28]

Measurement of outcome parameters

Most properly designed clinical trials have one principal outcome and several secondary outcome measures, which are all clearly defined before the study begins.[16] The use of one single principal outcome measures is recommended, as this increases the possibility of reaching a definite conclusion. Outcome measures usually relate to one of three things—namely, efficacy, safety, and quality of life issues.[20]

Documentation

Well-designed, pre-printed, and pre-bound clinical record forms must be custom-made for each study. Clinical record forms help minimise errors and variability and should be concise, instructive, and well organised. The response to questions on the clinical record forms (ie information entered) should be short and precise.[16] In the West, clinical record forms are made in triplicate with the sponsor, investigator, and archive holding one copy each. Subject compliance to the treatment protocol must also be assessed and documented in the clinical record forms.

Verification of data validity: monitoring

Monitors are appointed by the sponsor to independently oversee the progress of a trial. The monitors should ensure that the study is conducted, recorded, and reported in accordance with the protocol and GCP.[29] Trial monitoring is the single most important part of GCP and is essential for assuring data validity and reliability. The appointment of an independent and knowledgeable monitor should not worry an honest investigator whose task is actually being facilitated. The deployment of monitors to verify the validity of clinical data in therapeutic trials, despite its acknowledged importance and universal application in North America and western Europe, is still not widely practised locally. But it is anticipated that monitoring will become increasingly more frequent as the conduct of clinical trials becomes more sophisticated in Hong Kong and the rest of Asia.

Analysis of data and drawing of conclusions

Only an experienced and qualified biostatistician should analyse the clinical trial data. In many instances, there is difficulty in documenting a treatment difference statistically (ie type II error) due to small sample size.[16] Hence it is unethical to conduct a clinical trial using an inadequate sample size as the results will be inconclusive anyway. The patients and staff therefore undergo a meaningless exercise that has potential risks for all parties. To calculate the sample size, the biostatistician needs to know the study design, principal outcome measure, type of statistical tests to be used, the smallest treatment difference in outcome measure that can be documented as statistically different, and α (0.05) and β (0.10 or 0.20) values.[9]

In addition, it is also possible to not inform the statistician of the treatment grouping so that the statistician cannot analyse the data in a biased manner. This 'triple blinding' can also include the principal investigator so that the risks of producing biased conclusions are reduced.

The personnel involved in a clinical trial

The team of professionals and test subjects (patients) have to cooperate smoothly to ensure that a successful clinical trial is conducted (Box 3). The individuals involved include subjects, sponsor, principal investigator, monitor, Ethics Committee, supplier of trial medications or instruments, contract research organisation, and statistician.

Patients or trial subjects

Patients should be recruited after giving written informed consent in a manner approved by the institution's Ethics Committee. It must be stressed that patients have no moral, clinical, or legal obligation to

Box 3. The responsibilities of key clinical trials personnel

Personnel	Responsibility
Principal investigator	• must ensure that adequate time and resources are available and that appropriate patients are selected • obtain permission from the hospital and Ethics Committee, and obtain patient consent • respect patient confidentiality and manage the trial code without unnecessarily breaking the code • dispense, retrieve unused medicines, and maintain and complete research documents • properly collect, record, and report all data and supply these to the sponsor and monitor • report all adverse events and observe the following regarding each patient's care: (1) ensure provision of resuscitation (2) maintain medical care after the study and follow up incidental or study-related abnormalities (3) provide contact telephone number and a card for the attention of emergency medical personnel (4) maintain good clinical records and ensure that the usual medical attendant is agreeable to the patient's participation
Sponsor	• must provide insurance or indemnity and adequate resources to perform the study • maintain quality assurance and ensure that data are generated, documented, and reported as per GCP guidelines • provide the trial medications • alert the investigators to any new findings • handle adverse events, particularly serious ones
Subject	• patients have no moral or legal responsibility to undertake a trial • cooperation is therefore only gained by developing a good doctor-patient relationship
Monitor	• verify the investigators' qualifications, resources, technical capabilities, and supporting staff (eg sub-investigator) • verify the source document and other trial records and inform both the investigator and sponsor • report adverse events • provide written reports to the sponsor after each site visit

participate in any study. Patients must be reassured that withdrawal at any stage of the study is possible without the need to give any formal explanation and without affecting their subsequent treatment. Financial gain by a patient due to their participation in a trial is highly undesirable and unethical. The safety and comfort of the subject is of paramount importance to them and direct out-of-hours access to the principal investigator or his deputy must be made available. Concise but essential information about the study and its potential implications for an unexpected emergency should be clearly stated on a card given to the patient which they should carry. Cooperation is usually only gained after a friendly and honest relationship has been established by the investigator. Cooperation leads to compliance with the treatment protocol—an absolute necessity for the smooth running of any study. Violation of protocol ends in withdrawal of the patient and delays the progress of a study.

The principal investigator

The principal investigator should have support from a team of doctors, nurses, and other research personnel. The principal investigator usually delegates the day-to-day running of the study to a sub-investigator. Prior to beginning the study, the principal investigator must obtain Ethics Committee approval for the study protocol. A sub-investigator needs to be closely supervised, suitably qualified, and familiar with the GCP guidelines.[12-14] The sub-investigator can be a research assistant, nurse, research fellow or specialist trainee. The principal investigator must ensure that whenever appropriate, data are collected by the same support staff, to minimise inter-observer error. In addition, adequate training of the sub-investigator must be given so that the intra-observer bias is also reduced.

The sponsor

The sponsor is usually an organisation and is responsible for initiating, managing, and financing the study. The sponsor is usually in charge of designing the clinical trial, recruiting staff, and consulting with appropriate experts. Such experts typically include academic clinicians, clinical specialists, pharmacologists, pharmaceutical physicians, statisticians, lawyers, technicians, suppliers, and printers.

The sponsor should recruit qualified and respected investigators.[30] The sponsor should establish an independent data-monitoring committee to assess the progress, safety, efficacy end-points, and termination point of the study. Before signing the official agreement with the investigator, the sponsor should provide an updated

protocol and investigator's brochure. Sufficient data should be provided on the safety and efficacy of a drug, with specific reference to human studies, including route of administration, dosages, and duration of treatment.

The monitor

Monitors are appointed by the sponsor to oversee the progress of a trial.[31] They should ensure that the study is conducted, recorded, and reported in accordance with the protocol and GCP. Trial monitoring is the single most important part of GCP requirement and is essential to ensure data validity and reliability.

The Ethics Committee

A clinical trial must be accepted and monitored by the institution's Ethics Committee.[26] This should be an independent body comprising medical, scientific, and lay members, whose responsibility is to protect the rights, safety, and well-being of people involved in a clinical trial. The committee reviews all research protocols, consent forms, and suitability of the investigators.

Contract research organisations

Contract research organisations (CROs) are organised institutions (academic, commercial, or both) that act on behalf of a contracted sponsor to perform part or all of a clinical study; CROs usually have in-house capabilities for the design, recruiting of investigators, assurance of quality, monitoring, and construction of the final report. Many CROs are associated with university clinical units to facilitate the recruitment of patients and investigators. As they are essentially profit-making institutions, the cost of engaging the services of a CRO is usually substantial. The ultimate legal and moral responsibility for data accuracy and ethics must, however, rest with the sponsor. Clinical trials conducted by CROs are still rare in Hong Kong but a few major international CROs have recently established bases in south-east Asia.

Suppliers

These are usually in-house suppliers for the sponsor, especially if the latter is a pharmaceutical company. In studies that compare the efficacy of two drugs, however, there might be a need to obtain the other treatment arm from a rival pharmaceutical company. Some special measurements need special machines that have to be custom-made and maintained. The investigator must be absolutely certain that the trial and placebo medications are of the desired quality.

Statistician

The ICH GCP guidelines make it a necessity that an expert biostatistician be actively involved in the design and analysis of a clinical trial.[12-14] In addition, all clinical trial investigators should also have some basic knowledge of biostatistics.

Classical 'catches' in clinical trials

A number of conceptual errors, which are usually not deliberate, can arise in the administration of clinical trials. These are as follows: a biased principal investigator who designed a protocol with biased views; non-adherence to recruitment, assessment, or the treatment protocol; the priming of patients ('are you feeling better with the treatment?'); performing overanalysis of limited data other than the predetermined primary and secondary outcome measurements; and a change of assessor, equipment, or methodology during the study.

The local situation

Many well-designed studies are being conducted locally by academics as well as clinicians at various institutes. However, many of these, including therapeutic studies performed in collaboration with pharmaceutical companies, are not adequately funded. This means that the principal investigators and their affiliated personnel have to devote enormous efforts to many aspects of the studies that could be performed by a sub-investigator such as a research assistant. While the design of a study is frequently scientific and solid, there are still many studies that lack important elements such as randomisation, sample size calculation, and some form of blinding. Adequate data extraction is often achieved eventually, although the clinical data might not be documented in carefully-designed, answer-prompting, study-stage specific, and bound clinical record sheets. Analysis of data is usually performed by the principal investigators, who have some training in biostatistics, but this can be further improved if specialist clinical biostatisticians are consulted. Fortunately, the relative lack of availability of the latter in Hong Kong and the surrounding region is now improving, particularly at the two medical faculties in Hong Kong. Although the GCP guidelines specifically stipulate the need for data monitoring and verification, the practice of monitoring is still rare in Hong Kong. The situation might improve in the near future as local training courses have recently become available.

Despite the above local constraints and particularly, the lack of adequate funding and professional monitors, good-quality clinical trials can still be performed adequately by local investigators. The local situation should not bar principal investigators from designing a solid study—this requires examination of the background knowledge, inclusion of an adequate control group,

recognition of the need for prospective data, and careful construction of a detailed protocol. Lack of resources should not discourage investigators from properly defining outcome measures, recruiting subjects, and designing clinical record sheets that are user-friendly and unambiguous. The lack of monitoring, data verification, and funding in many studies can only be improved when pharmaceutical companies recognise that these are essential elements of the GCP and therefore important to the generation of ethical and solid data. Investigators should reiterate this to their pharmaceutical counterparts so that a culture of GCP and adequate funding can be generated locally.

Conclusion

The gold standard therapeutic trial is a 'randomised, double-blind, placebo-controlled study with data monitoring and prestudy sample size calculation'. In a GCP-approved clinical therapeutic trial, it is typical that the principal investigator, independent statistician, and the sponsor have refined the study protocol and ensured that the study's projected end-points are scientifically worthy and measurably sensitive. The protocol should be approved by the institutional Ethics Committee, which should also scrutinise the contents of the patient consent form. The monitor and sponsor should independently verify the expertise, availability of target patients, and equipment claimed by the principal investigator before the study commences. The monitor should visit the site regularly to verify data validity by directly referring to the source documents (eg patient's clinical notes and original test reports). On completion of the study, the data should be sent to the independent expert biostatistician for analysis, ideally with blinding of the treatment protocol. The principal investigator can then summarise the results and draw the relevant conclusions. The source documents may have to be archived for many years after completion of the study, before disposal can be permitted.

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