Pharmaceutical Medicine

The physicians' role in the clinical development of new medicines

S.J. Warrington & S.I. Ankier

Charterhouse Clinical Research Unit Ltd., 'Boundary House', 91–93, Charterhouse Street, London, EC1M 6HR, UK.

Introduction

At one time the process of testing new medicines was the province mainly of physicians in teaching hospitals, but this is no longer so: physicians in district hospitals and in general practice are increasingly involved because they are caring for the patients eligible for the clinical trials. In this article we review briefly the early stages in the development of a new drug, or 'new chemical entity' (NCE), and consider especially those aspects which are important to the physician participating in that process.

Preclinical development of new medicines

After screening for pharmacological effects in both isolated tissues and whole animals, promising NCEs are subjected to a battery of acute and chronic toxicological tests in animals.^{1,2} In acute testing, increasing single doses are given to identify target organ(s) for toxicity and to assess the ratio between effective and toxic doses. In chronic testing, at least 2 species must be studied, 1 of which must be a non-rodent; the NCE must be given by the route intended to be used in man, and of the 3 dose levels tested the highest should produce some signs of toxicity. At the end of chronic toxicity tests, histological examinations are made of all important internal organs.

Before an NCE is studied in volunteers or patients, exposure in animals should exceed the intended duration of exposure in human. In the United Kingdom animal studies lasting 14 days allow 1 dose (or several small doses within 1 day) of a NCE in man while 28 days' exposure in animals permits repeated dosing in man lasting up to 10 days. For up to 30 days' exposure in man, animal toxicity studies lasting 90 days are required. Mutagenicity tests are used to detect possible carcinogenic effects and are done before first administration to man. Fertility and teratology

studies to identify possible pre-, peri- and post-natal toxicity are completed before administration to women of child-bearing potential. Carcinogenicity studies are performed late in the development of a NCE.

Phases of drug development in man

It is conventional to divide the development of a NCE in man into 4 Phases.^{3,4} Phase I studies are performed in healthy volunteers and include the first administration of single and repeated doses to assess tolerability, pharmacokinetics (absorption, distribution, metabolism and excretion) and, if possible, pharmacodynamic activity.

Phase II studies aim to show possible therapeutic effects in small groups of patients. Encouraging results lead to Phase III studies in which more patients, both in hospital and in general practice, are studied to confirm the therapeutic effect, to establish dosage range and interval and to assess toxicity. Successful Phase III studies lead to the marketing of a NCE when the data have been assessed by the Committee on Safety of Medicines (CSM) and a product licence has been obtained.

Once a new medicine is on the market, Phase IV research is conducted. This includes comparisons of efficacy with established compounds and, commonly, further studies of different dosage regimens. Phase IV also includes formal post-marketing surveillance (PMS) and, in the UK, an analysis of adverse events reported via the 'red alert' and Yellow Card systems. All practising clinicians should use these systems to report adverse events to the Department of Health (DoH), and thus are involved in Phase IV of drug development.

Involvement of physicians

Phase I studies are conducted by specially trained and experienced physicians in hospitals, independent clinical research units, or the premises of the larger pharmaceutical companies. It is in Phase II, III and IV clinical trials that clinicians are most

Correspondence: S.J. Warrington M.A., M.B., B.Chir., M.D., M.R.C.P.

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likely to be invited to participate. Any clinician who is intending to perform a study of a pharmaceutical product in patients must direct close attention to these vital areas: (1) DoH authorization for the study; (2) Investigator's Brochure; (3) study protocol; (4) case record book; (5) ethics; (6) consent; (7) funding; (8) indemnity.

1. Licensing Authority authorisation

In the UK, NCEs are studied in healthy volunteers without reference to the Licensing Authority, whereas all studies of unlicensed medicines in patients require some form of scrutiny by the DoH. This will take one of three possible forms:

Investigator's exemption This can only be granted, on a 'named patient' basis, where the clinician has himself approached the pharmaceutical manufacturer with a proposal for the use of a NCE in patients. In practice this is rare, and almost always either a Clinical Trial Certificate or Clinical Trial Exemption Notification is required.

Clinical Trial Certificate (CTC) This is granted by the DoH upon the recommendation of the CSM after assessment of full pharmaceutical, chemical, pharmacological and toxicological data, and of any studies which have been carried out in healthy volunteers. There may be a considerable delay between submission of data and granting of a CTC because of the great bulk of information to be considered by the CSM and its advisers, and this led to the introduction of the Clinical Trial Exemption Notification scheme.

Clinical Trial Exemption (CTX) Notification The application for a CTX resembles that for a CTC except that only summaries of data are submitted. The application is reviewed by assessors at the DoH and the CSM is not involved. The fate of a CTX notification is normally communicated within 35 days of acceptance of the data by the DoH, and this is much quicker than the CTC procedure. Submission of a CTX notification must include the study protocol and names of participating clinicians. The potential investigator, therefore, has to give provisional agreement to perform the study before a CTX can be obtained.

2. Investigator's Brochure

This vital document contains details of chemistry and formulation, pharmacy and toxicology, and reports on any studies in healthy volunteers. Neither the CTC nor the CTX procedure absolves the investigator from the ultimate responsibility for the welfare of his patients, and he must, therefore, read the Investigator's Brochure and assure himself

that the general and specific pharmacology of the compound has been well defined, that its toxicity in animals is acceptable, and that any previous administration to man supports the proposed investigation. If any points in the investigator's brochure require clarification, the manufacturer will provide copies of full reports upon request. If doubts persist, the opinion of an external reviewer should be sought.

3. The study protocol

A good protocol contains the answers to every foreseeable question that might arise during and after the study and is therefore long and, in places, uninteresting. A well thought-out protocol will, however, prove its worth when queries do arise. A condensed version detailing the day-to-day requirements is helpful. The intricacies of protocol generation have been well described elsewhere^{5,6} but the practical value of certain sections is worthy of emphasis.

(a) *The front page:* names, addresses and telephone/ bleep numbers of the relevant parties can save time and frustration when problems arise. Twenty-four hour emergency contact procedures should be specified.

(b) *The Introduction* may give sufficient background information to make referral to the Investigator's Brochure unnecessary except for points of detail.

(c) *Aim of study.* As a rule, there should only be one main study objective. Defining this section precisely concentrates the mind on the exact question(s) which the study must answer.

(d) *Eligibility criteria.* It is vital to list in detail the features which are required in patients to be included or excluded from the study. The most common problems in practice are whether other medical, surgical or psychiatric conditions, or treatment with a particular drug or class of drugs, should disqualify the patient. Deciding on what features constitute the disease in question is often highly educational.

(e) *Patient numbers.* The physician must consider at the planning stage whether he is likely to see enough eligible patients. It is usual to over-estimate the availability of suitable patients, and before agreeing to participate in a study the physician might keep a 'dummy-recruitment-diary' for a few months to check this matter.

If insufficient patients are available to any one investigator, other investigators must share the work and the study is a 'multicentre' one. Complete uniformity between centres is unattainable but meetings of participating physicians before, during and after the study can help to reduce the differences to an acceptable level.

(f) *Treatments.* The identity of the treatments should be double-blind (i.e. unknown to both the investigator and the patient) in all comparative studies, unless this is impossible. This section of the protocol should state how 'blindness' is to be maintained, and how the treatments are to be packaged and labelled. Will the patients be able to understand the instructions, and will they be able to open the containers? If the container is lost, will the labelling allow it to be returned to the study physician, pharmacist or study sponsor?

Sealed randomization codes must be available so that the identity of the treatment may be discovered, in an emergency. The identity of a treatment should not be disclosed prematurely in any other circumstances since this may bias the interpretation of the study.

(g) *'Run-in' or 'wash-out' periods.* Many studies incorporate a preliminary phase during which the patient's previous treatment is withdrawn. The physician must consider carefully whether this is safe. A further problem with run-in periods is that some otherwise eligible patients may fail to meet the inclusion criteria after their treatment has been withdrawn.

(h) *Study procedures.* This section should answer all reasonable questions about how the study will actually be carried out. It is particularly important that the methods of measuring study end-points should be described comprehensively. For example, will the blood pressure be measured by a standard mercury-in-glass sphygmomanometer or by a random zero machine, and will the diastolic pressure be taken as Phase IV or V of the Korotkov sounds? Will anyone other than the physician in charge of the study be allowed to make the assessments? A suitably experienced research nurse might do the more routine measurements.

This section should also specify what will be done if the patient cannot attend on the correct day during a study. A few days' latitude is usually tolerable, but the limit of acceptability should be decided in advance.

If blood samples are to be taken, is plasma or serum required, and is a suitable centrifuge available? If not, the study sponsor may be able to loan or donate a machine. Many protocols fail to warn against the use of water soluble ink for the labelling of samples; they should certainly do so, since a bag of anonymous plasma samples is a tragedy for all concerned.

(i) *Adverse events.* The procedure for recording adverse events should be set out. The sponsor must be informed immediately of all serious events, but all adverse events should be recorded. As the development of the drug proceeds, these records build up into a valuable database which will help to establish the true adverse effects of the drug.

(j) *Withdrawals.* The patient always retains the right to withdraw from the study at any time without prejudicing his medical care and without giving a reason. The physician may also withdraw a patient from the study, but must record the reason.

(k) *Laboratory analysis.* The analysis of drug concentrations in body fluids is normally arranged by the study sponsor, but haematology, biochemistry and urinalysis may be done by a central or a local laboratory; this should be specified. If local hospital laboratories are to be used, they should be informed that the study is being undertaken and there should be provision for payment for any tests which are not part of the patients' routine clinical care.

(l) *Statistical analysis* will usually be undertaken by the sponsor, but the physician may retain the right to conduct his own analysis in addition. It is a good discipline for the protocol to specify in some detail the statistical tests to be used, as this is a powerful defence against the accusation that the data have been 'dredged' or 'massaged' after the study is finished.

(m) *Report and publication.* Few physicians are equipped to generate a complete report of a project, but the

protocol may specify that a report on the clinical aspects of the study is required.

A section dealing with publication of the results reduces the possibility of misunderstanding of this sensitive topic. No self-respecting study sponsor would attempt to prevent publication of data, but the protocol may well state that the sponsor should have the opportunity to comment on any manuscript before it is submitted for publication. This is entirely reasonable, and is in any case no more than courtesy demands.

4. The case record books

All the data from a patient in a clinical research study should be recorded upon a series of forms which are collected together into a case record book. A well thought-out case record book can make the difference between the success and failure of a study. The relevant forms should be arranged in chronological order within the book, so that the clinician can make the right observations and recordings at the right time and with the minimum of page turning. Carefully placed prompts drawing attention to the most important points in the protocol and/or summary tables of required activities can greatly reduce the risk of errors or omissions. This may make the case record book rather bulky, but it will save time in a busy clinic and increase the likelihood of success in the long run.

If the case record book is not satisfactory, ask if it can be improved; the study sponsor will welcome any constructive suggestions which will help the study to run well.

Entries in case record books are best made in black ball point pen, since it photocopies well, it produces reliable copies with 'no carbon required' copying paper and, unlike fountain or fibre tip pens, the ink does not run when exposed to water, blood or urine – all of which tend to be found in substantial quantities in the environs of clinical studies.

Any error should be rectified not by alteration or obliterating fluid but by a crossing out with a single line and writing the correct entry nearby, with the investigator's dated initials appended. This procedure may seem laborious, but it is required by many regulatory authorities who will ultimately inspect the data.

A properly completed case record form is a jewel of inestimable price, and should not be entrusted to the ordinary postal service until it has been photocopied or the 'no carbon required' copy sheets removed.

5. Ethics

The internationally accepted ethical standards of clinical studies are contained in the Declaration of Helsinki⁷ which should be appended to the pro-

tocol. Regulatory authorities now require that the study be approved by the appropriate ethics committee, however banal and uncontroversial the study may appear.

The physician must genuinely believe that the new treatment to be studied may be in some way superior to the old – better therapeutic effect, improved tolerability, palatability or convenience of dosing regimen. If he does not accept this possibility, then he cannot ethically agree to his patient being randomly allocated to one regimen or another. It is, of course, unrealistic to expect that the new treatment will be superior to the old for *every* patient; there should merely be reasonable grounds for expecting that it will be better for *some* patients.

6. Consent

The study protocol should require that the patient (or his or her guardian) gives consent in writing to participate in the study. Clinicians occasionally protest that this makes consent harder to obtain, but this stance is difficult to defend against the accusation that verbal consent is only easier to obtain because less full information has been imparted to the patient before it is given. Valid consent must be both *informed* and *freely given*, and neither of these criteria are easily satisfied in the context of the doctor–patient relationship. Clinicians do not normally emphasize the possible adverse effects of a treatment and so naturally tend to present a somewhat rosy picture of the hazards of participating in a study; and there are subtle pressures upon the patient to agree to the doctor's request for help in a study. Although there are no easy solutions to these problems, consent is more likely to be informed if the patient is provided with a written information sheet to read before making up his mind. The final consent statement should emphasize that participation is voluntary, will not affect the patient's medical care, and can be terminated at any time if the patient wishes. The patient should be allowed to keep the information sheet for future reference.

7. Funding

Patients are not paid a fee for participating in a study, but a sponsor may reasonably be required to reimburse their travel expenses. The physician is entitled to an appropriate fee for studying patients, but ideally this should not be the main motive for doing clinical research. General practitioners are independent contractors and may therefore without qualms accept fees for additional work. National Health Service employees are in a more difficult position, but since the extra time spent on a research project during working hours usually

means that other work has to be done in the evening or weekends, it is right that this should be rewarded.

The sponsor may be prepared to pay very high fees to physicians for studying patients, particularly in specialities such as psychiatry where suitable investigators are in short supply. This may be inevitable in a 'free market' for physicians' services, but it could create ethical difficulties: it could be argued that a high fee per patient studied might induce the physician to include patients who were unsuitable or ineligible, or to impart incomplete information about the study in order to obtain the patient's consent. Thus ethics committees might reasonably request details of payments to investigators before giving approval to a project.

Physicians should avoid participating in two or more studies requiring similar patients but having different sponsors. In these circumstances, the fee per patient would assume excessive importance in determining the study into which each patient is recruited.

Investigators' fees are often paid directly into departmental accounts, and in that case the physician may charge whatever the 'market' will bear. Excessive dependence of academic departments upon commercial sponsors is not a healthy state of affairs, but seems unavoidable in the light of reduced funding of research by the taxpayer. The study sponsor may be willing to fund a research post for a limited period, rather than paying fees on a *per capita* basis. If such comfortable arrangements are to continue, it is vital that maximum effort is made by all concerned to complete the sponsor's project satisfactorily. Failure to do this will make it much harder in future for academic departments to secure such agreements with the pharmaceutical industry.

Financial arrangements should always be agreed in writing before a study commences.

Part of the reward for carrying out a study may be the opportunity to present the results at a conference in some exotic and attractive part of the world, at the expense of the sponsor. This may attract criticism if the arrangements for travel and hospitality are unduly lavish – as, for example, when the participants were transported to the meeting venue by Orient Express rather than by air.

8. Indemnity

Pharmaceutical sponsors of a clinical study should provide a statement that compensation will be paid to the patient, without a requirement that negligence be proved, if a serious, lasting, or disabling injury occurs during the study and if there is a balance of probability that it was attributable to the sponsor's drug.⁹

The study monitor

The initial contact between the pharmaceutical company and the clinician is often made by a pharmaceutical physician, but when the details of a study have been agreed the responsibility for monitoring the study usually passes to a clinical research associate (CRA) who normally has a scientific rather than medical training. Before the first patient is recruited, the CRA should visit the clinician, check all relevant facilities including the normal laboratory ranges at a centre, meet all participating staff, go through all the requirements of the protocol and case record form in detail and obtain the clinician's Curriculum Vitae. Once the study is under way, the CRA should visit the clinician at least every 6 weeks to ensure accurate collection of data, and should be available at other times on the telephone. The clinician should not feel in any way threatened by these visits, and must allocate sufficient time for discussions during which any problems which arise during the course of the study may be ironed out and any misunderstandings in the interpretation of the protocol and the completion of the record forms may be clarified. The record forms will probably be checked in minute detail, which at first may seem irritating but, since the completed record form represents a lot of hard work by the clinician, the extra effort involved in getting it exactly right is well worthwhile. Reference to source documents in order to verify data is similarly good practice and should not be resisted.

At the end of the study, the CRA requires the investigator's assistance to account for the amount of medication used and the co-operation of the pharmacist should be encouraged here. If appropriate, arrangements for the transport of biological samples to the analytical laboratory will be discussed with the CRA.

It cannot be emphasized too strongly that the help of the CRA should be sought whenever problems arise during a study. Carrying out a clinical research study involves a major effort by both the pharmaceutical company sponsor and clinician, and the study monitor will always be keen to sort out any problems which threaten the success of the enterprise.

Good Clinical Research Practice (GCRP)

The term 'Good Clinical Practice' (GCP) was coined by the Food and Drug Administration

(FDA) in the USA to describe a set of rules which was formulated after it was found that data submitted to them had been falsified. GCP does not have the force of law even in the USA, but is widely respected as a procedure to standardize and to improve the performance of clinical studies. Many studies are now carried out to GCP 'requirements' but some aspects of GCP do not transplant well from the USA to other cultures. The Association of the British Pharmaceutical Industry recently issued Guidelines on Good Clinical Research Practice (GCRP) which are a UK equivalent of GCP.¹⁰ The GCP and GCRP proposals set out the obligations of study sponsors, monitors, and clinical investigators, and include recommendations concerning Ethics Committees, informed consent procedures, reporting of adverse events and the archiving of data. These proposals do not include any rules or recommendations concerning the clinical care of patients and GCP is, therefore, a misnomer: the terms GCP and GCRP refer only to the *conduct* of research projects. Most of the elements of GCP or GCRP are not controversial, but clinicians will probably notice that their mention is usually associated with an increase in the bureaucratic aspects of the project.

A clinical research study which is not carried out to an adequate standard is unethical, since patients will be exposed to inconvenience, discomfort or hazard in exchange for a benefit which will be less than that which could have been achieved. GCP and GCRP are thus to be welcomed, since they encourage a uniformly high standard of work in the development of new pharmaceuticals.

Conclusions

The development of new medicines has generated tremendous benefits for patients in the past, and there is every reason to suppose that it will continue to do so in the future. New drugs cannot conceivably be developed without the help of practising physicians. The number and complexity of clinical trials required in the development of a medicine are steadily increasing, and more physicians will be invited to participate in the process. Carrying out a successful clinical trial is a challenging and stimulating discipline. We hope that this article will encourage many physicians to take up the challenge.

References

1. Steelman, R.L. Drug safety evaluation and implications for clinical investigation. In: Matoren, G.M. (ed) *The Clinical Research Process in the Pharmaceutical Industry*. Marcel Dekker, New York, 1984, pp 273–285.
2. Brimblecombe, R.W. & Dayan, A.D. Preclinical toxicity testing. In: Burley, D.M. & Binns, T.B. (eds) *Pharmaceutical Medicine*. Edward Arnold, London, 1985, pp. 18–38.
3. Cato, A.E. & Cook, L. Clinical research. In: Matoren, G.M. (ed) *The Clinical Research Process in the Pharmaceutical Industry*. Marcel Dekker, New York, 1984, pp. 217–238.
4. Burley, D.M. & Glynn, A. Clinical trials. In: Burley, D.M. & Binns, T.B. (eds) *Pharmaceutical Medicine*. Edward Arnold, London, 1985, pp. 18–38.
5. Spilker, B. Developing and writing clinical protocols. In *Guide to Clinical Studies and Developing Protocols*. Raven Press, New York, 1984, pp. 87–211.
6. Fidler, K. & Koch, I. The protocol. In: Glenny, H & Nelves, P. *Handbook of Clinical Drug Research*. Blackwell Scientific Publications, Oxford, 1986, pp. 196–226.
7. DECLARATION OF HELSINKI: 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects'. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983; Publ. The World Medical Association, Inc. Ferney-Voltaire, France.
8. *The Relationship between Physicians and the Pharmaceutical Industry*. Royal College of Physicians, London, 1986.
9. *Guidelines: Clinical Trials – Compensation for Medicine-Induced Injury*. ABPI, London, 1983.
10. *Guidelines on Good Clinical Research Practice*. ABPI, London, 1988.