



Practical addenda

Addendum 4: British guidelines for “postmarketing surveillance studies”

In the UK, guidelines for company-sponsored “postmarketing surveillance studies” have been developed by a joint committee representing the pharmaceutical industry (ABPI = Association of the British Pharmaceutical Industry), the BMA (British Medical Association), the British Health Authority (CSM = Committee on Safety of Medicines) and the Royal College of General Practitioners. These guidelines have been widely distributed, especially to the medical profession by a publication in the *British Medical Journal* (Volume 296 of 6 February 1988) and via the ABPI Data Sheet Compendium.

These guidelines are useful when one wants to conduct such a type of study. They should ensure that ethical principles are adhered to.

The guidelines have recently been revised. They are reprinted here (Fig. 1) from the “Current Problems” issue of February 1994 (“Current Problems” is a CSM publication).

SAFETY ASSESSMENT OF MARKETED MEDICINES (SAMM) GUIDELINES

Introduction

It is well-recognised that there is a continuous need to monitor the safety of medicines as they are used in clinical practice. Spontaneous reporting schemes (e.g. the UK yellow card system) provide important early warning signals of potential drug hazards and also provide a means of continuous surveillance. Formal studies to evaluate safety may also be necessary, particularly in the confirmation and characterisation of possible hazards identified at an earlier stage of drug development. Such studies may also be useful in identifying previously reactions.

Scope of Guidelines

These guidelines apply to the conduct of all company-sponsored studies which evaluate the safety of marketed products. They take the place of previous guidelines on post-marketing surveillance which were published in 1988 (BMJ, 296 : 399-400). Studies performed under those guidelines were found to have some notable limitations (BMJ, 1992, 304 : 1470-1472) and these new guidelines have been prepared in response to the problems identified. The major changes may be summarised as follows:

- (1) The scope of the guidelines has been expanded to include all company-sponsored studies which are carried out to evaluate safety of marketed medicines. It should be emphasised that this includes both studies conducted in general practice and in the hospital setting. The name of the guidelines has been changed to reflect the emphasis on safety assessment rather than merely surveillance.
 - (2) The guidelines have been developed to provide a framework on which a variety of data collection methods can be used to improve the evaluation of the safety of marketed medicines. Whilst it is recognised that the study design used needs to be tailored to particular drugs and hazards, the guidelines define the essential principles which may be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need to review regularly these guidelines to ensure that they reflect advances made in the assessment of drug safety. The guidelines have been formulated and agreed by a Working Party which includes representation from the Medicines Control Agency (MCA), Committee on Safety of Medicines (CSM), Association of the British Pharmaceutical Industry (ABPI), British Medical Association (BMA) and the Royal College of General Practitioners (RCGP). Other guidelines exist for the conduct of "Phase IV clinical trials" where the medication is provided by the sponsoring company (see section 2(b) below). Some of these studies will also meet the definition of a SAMM study (see below) and should therefore also comply with the present guidelines.
1. **Definition of Safety Assessment of Marketed Medicines**
 - (a) Safety assessment of marketed medicines (SAMM) is defined as "a formal investigation conducted for the purpose of assessing the clinical safety of marketed medicine(s) in clinical practice".
 - (b) Any study of a marketed drug which has the evaluation of clinical safety as a specific objective should be included. Safety evaluation will be a specific objective in post-marketing studies either when there is a known safety issue under investigation and/or when the numbers of patients to be included will add significantly to the existing safety data for the product(s). Smaller studies conducted primarily for other purposes should not be considered as SAMM studies. However, if a study which is not conducted for the purpose of evaluating safety unexpectedly identifies a hazard, the manufacturer would be expected to inform the MCA immediately and the section of these guidelines covering liaison with regulatory authorities would thereafter apply.
 - (c) In cases of doubt as to whether or not a study comes under the scope of the guidelines the sponsor should discuss the intended study plan with the MCA.
 2. **Scope and Objectives of SAMM**
 - (a) SAMM may be conducted for the purpose of identifying previously unrecognised safety issues (hypothesis-generation) or to investigate possible hazards (hypothesis-testing).
 - (b) A variety of designs may be appropriate including observational cohort studies, case-surveillance or case-control studies. Clinical trials involving systematic allocation of treatment (for example randomisation) may also be used to evaluate the safety of marketed products. Such studies must also adhere to the current guidelines for Phase IV clinical trials.
 - (c) The design to be used will depend on the objectives of the study, which must be clearly defined in the study plan. Any specific safety concerns to be investigated should be identified in the study plan and explicitly addressed by the proposed methods.
 3. **Design of studies**

Observational cohort studies

 - (a) The population studied should be as representative as possible of the general population of users, and be unselected unless specifically targeted by the objectives of the study (for example a study of the elderly). Exclusion criteria should be limited to the contraindications stated in the data sheet or summary of product characteristics (SPC). In prospective studies the prescriber should be provided with a data sheet or SPC for all products to be used. Where the product is prescribed outside the indications on the data sheet, such patients should be included in the analysis of the study findings.
 - (b) Observational cohort studies should normally include appropriate comparator group(s). The comparator group(s) will usually include patients with the disease/indication(s) relevant to the primary study drug and such patients will usually be treated with alternative therapies.
 - (c) The product(s) should be prescribed in the usual manner, for example on an FP10 form written by the general practitioner or through the usual hospital procedures.
 - (d) Patients must not be prescribed particular medicines in order to include them in observational cohort studies since this is unethical (see section 15 of the "Guidelines on the Practices of Ethics Committees in Medical Research involving Human Subjects", Royal College of Physicians, 1990).
 - (e) The prescribing of a drug and the inclusion of the patient in a study are two issues which must be clearly separated. Drugs must be prescribed solely as a result of a normal clinical evaluation, and since such indications may vary from doctor to doctor a justification for the prescription should be recorded in the study documents. In contrast, the inclusion of the patient in the study must be solely dependent upon the criteria for recruitment which have been specifically identified in the study procedures. Any deviation from the study criteria for recruitment could lead to selection bias.
 - (f) The study plan should stipulate the maximum number of patients to be entered by a single doctor. No patient should be prospectively entered into more than one study simultaneously.

Case-control studies

- (g) Case-control studies are usually conducted retrospectively. In case-control studies comparison is made between the history of drug exposure of cases with the disease of interest and appropriate controls without the disease. The study design should attempt to account for known sources of bias and confounding.

Case-surveillance

- (h) The purpose of case-surveillance is to study patients with diseases which are likely to be drug-related and to ascertain drug exposure. Companies who sponsor such studies should liaise particularly closely with the MCA in order to determine the most appropriate arrangements for the reporting of cases.

Clinical trials

- (i) Large clinical trials are sometimes useful in the investigation of post-marketing safety issues and these may involve random allocation to treatment. In other respects, an attempt should be made to study patients under as normal conditions as possible. Exclusion criteria should be limited to the contraindications in the data sheet or SPC unless they are closely related to the particular objectives of the study. Clinical trials must also adhere to the current guidelines for Phase IV clinical trials (see 2(b) above). Studies which fulfil the definition of SAMM but are performed under a clinical trial exemption (CTX) or under the clinical trial on a marketed product (CTMP) scheme are within the scope of these guidelines.

4. Conduct of Studies

- (a) Responsibility for the conduct and quality of company-sponsored studies shall be vested in the company's medical department under the supervision of a named medical practitioner registered in the United Kingdom, and whose name shall be recorded in the study documents.
- (b) Where a study is performed for a company by an agent, a named medical practitioner registered in the United Kingdom shall be identified by the agent to supervise the study and liaise with the company's medical department.
- (c) Consideration should be given to the appointment of an independent advisory group(s) to monitor the safety information and oversee the study.

5. Liaison with Regulatory Authorities

- (a) Companies proposing to perform a SAMM study are encouraged to discuss the draft study plan with the Medicines Control Agency (MCA) at an early stage. Particular consideration should be given to specific safety issues which may require investigations.
- (b) Before the study commences a study plan should be finalised which explains the aims and objectives of the study, the methods to be used (including statistical analysis) and the record keeping which is to be maintained. The company shall submit the study plan plus any proposed initial communications to doctors to the MCA at least one month before the planned start of the study. The MCA will review the proposed study and may comment. The responsibility for the conduct of the study will, however, rest with the sponsoring pharmaceutical company.
- (c) The company should inform the MCA when the study has commenced and will normally provide a brief report on its progress at least every six months, or more frequently if requested by MCA.
- (d) The regulatory requirements for reporting of suspected adverse reactions must be fulfilled. Companies should endeavour to ensure that they are notified of serious suspected adverse reactions and should report these to the MCA within 15 days of receipt. Events which are not suspected by the investigator to be adverse reactions should not be reported individually as they occur. These and minor adverse reactions should be included in the final report.
- (e) A final report on the study should be sent to the MCA within 3 months of follow-up being completed. Ideally this should be a full report but a brief report within 3 months followed by a full report within 6 months of completion of the study would normally be acceptable. The findings of the study should be submitted for publication.
- (f) Companies are encouraged to follow MCA guidelines on the content of progress reports and final reports.

6. Promotion of Medicines

- (a) SAMM studies should not be conducted for the purposes of promotion.
- (b) Company representatives should not be involved in SAMM studies in such a way that it could be seen as a promotional exercise.

7. Doctor Participation

- (a) Subject to the doctor's terms of service, payment may be offered to the doctor in recompense for his time and any expenses incurred according to the suggested scale of fees published by the BMA.
- (b) No inducement for a doctor to participate in a SAMM study should be offered, requested or given.

8. Ethical Issues

- (a) The highest possible standards of professional conduct and confidentiality must always be maintained. The patient's right to confidentiality is paramount. The patient's identity in the study documents should be codified and only his or her doctor should be capable of decoding it.
- (b) Responsibility for the retrieval of information from personal medical records lies with the consultant or general practitioner responsible for the patient's care. Such information should be directed to the medical practitioner nominated by the company or agent, who is thereafter responsible for the handling of such information.
- (c) Reference to a Research Ethics Committee is required if patients are to be approached for information, additional investigations are to be performed or if it is proposed to allocate patients systematically to treatments.

9. Procedure for Complaints

A study which gives cause for concern on scientific, ethical or promotional grounds should be referred to the MCA, ABPI and the company concerned. Concerns regarding possible scientific fraud should be referred to the ABPI. They will be investigated and, if appropriate, referred to the General Medical Council.

10. Review of Guidelines

The Working Party will review these guidelines as necessary.

Source: Current Problems, February 1994

Fig. 1.