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Good practice in the postmarketing surveillance of medicines

• R.H.B. Meyboom

Introduction

It is now generally recognized and accepted that there is a need for Good Clinical Trial Practice (GCP), to ensure that clinical drug trials are, in ethical and scientific respects, properly conducted [1-2]. It has taken decades, however, until general agreement with regard to GCP was reached. A clinical trial concerns a medically very delicate situation: the use of an experimental treatment, simultaneously aiming at the cure (or diagnosis) of a patient and the demonstration of the efficacy and safety of that treatment. GCP is primarily concerned with the protection of the rights, interests and responsibilities of individuals, i.e. patients, investigators, and (often) the pharmaceutical company concerned. Important interests of the patients are the informed consent procedure, justification of predictable risks and inconveniences, scientific efficiency (i.e. the potential for reaching sound conclusions with the smallest amount of data), and appropriate measures with regard to treatment, insurance and compensation if a serious untoward effect occurs. Ethics committees ensure that trials are conducted according to GCP and to the Declaration of Helsinki (World Medical Association, June 1964). When a patient has consented to participate in a trial, all (anonymised) data relevant to his treatment are assumed to become the property of the investigator or sponsor of the study. The development of new medicines and the scientific quality of clinical trials are obviously of great importance to public health, but in GCP the public interest is only a secondary issue.

When a new drug is approved there is sufficient knowledge available to enable appropriate decision making regarding the treatment of individual patients. Paradoxically but inevitably, however, there is at the same time often some uncertainty with regard to the possible side effects of the drug or its safety (and efficacy) in the long term use in the population at large. Much of our knowledge of medicines comes available only during the years after introduction. To illustrate this, in table 1 a review is given of aspects of marketed medicines that often need further study. The clinical trial is a well developed and understood instrument [3]. The study of marketed medicines, on the other hand, is still in a developmental stage and many problems involved have only partly been solved.

Postmarketing surveillance

The Health Council in the Netherlands has defined postmarketing surveillance (PMS) as 'the systematic surveillance and scientific study of all intended and unintended effects of medicines on human health, after their release for marketing' [4]. It was added that 'its aim is to obtain data of scientific quality for the rational and safe use of medicines'. In this definition and in the context of this paper PMS refers to pharmacovigilance as well as to pharmacoepidemiology.

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Abstract

In addition to Good Clinical Trial Practice for the study of experimental drugs, regulations are also needed for good practice in the assessment of medicines after approval (Good PMS Practice, GPP). GPP has to protect the interests of public health at large as well as those of individual patients, investigators and pharmaceutical companies. GPP may be the natural way to solve threatening conflicts between privacy legislation and the public interest.

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Table 1 *Review of subjects of interest in the post-marketing evaluation of medicines*

1. Fine-tuning of dosage recommendations
2. Reappraisal of indications (extension or restriction)
3. Drug use and drug users characteristics
4. Assessment of long-term efficacy (e.g. in the case of surrogate endpoints)
5. Assessment of side effects:
 - 5.1. Detection of unexpected side effects and interactions
 - 5.2. Identification of risk factors
 - 5.3. Quantitative measurement of (un)safety
 - 5.4. Long term safety/toxicity
 - 5.5. Study of potential risk groups (e.g. children, elderly, pregnancy)
 - 5.6. Detection of unexpected beneficial effects
6. Further pharmacological and mechanistic studies
7. Detection of pharmaceutical defects and counterfeit drugs
8. Dangers of misuse (intentional and accidental intoxication, dependence)
9. Quality of life and utility assessment
10. Collection of data needed for cost assessment

The term pharmacovigilance is often used more specifically for the detection and prevention of adverse reactions [5], i.e. monitoring and early warning. PMS faces many different problems, of scientific, ethical, logistic, legal and financial nature. Through the years a variety of methods and systems have been developed, which can roughly be distinguished into 'spontaneous reporting' in all its different shapes, and the various epidemiological approaches (see table 2) [6-8]. All have specific advantages and shortcomings and new ways may be envisaged in the future. Spontaneous reporting, for example, is mainly effective in the detection of characteristic adverse reactions with a suggestive time relationship but is of limited use in estimating reaction frequency [9]. PMS is still under development and there is as yet some uncertainty into how much detail we will - scientifically, ethically and financially - be able to measure the balance of benefits and risks of medicines. For less affluent countries, the exact and costly measurement of the risks of efficacious drugs may even remain a luxury.

Table 2 *Methods for studying marketed medicines [6-8]*

1. Spontaneous reporting
2. Intensive hospital monitoring
3. Prescription event monitoring
4. Case control studies and case control surveillance
5. Follow-up studies (with or without control group)
6. Record linkage and large linked data resources
7. Drug use and users studies
8. Studies using disease registers

Burden of proof

At the moment when a medicine is approved by the competent authority many changes take place. The drug is no longer experimental but has (legally) become an established treatment. Its users no longer are experimental patients, monitored by the precautions of the trial and the provisions of GCP. Instead, the experiences with the drug are from now on more or less hidden from view because of medical and pharmaceutical secrecy. From the medical point of view, on the other hand, a new drug only slowly loses its experimental character during the years after introduction.

Before the registration of a medicine, the company has to meet the requirements put forward by the regulatory authority and to provide any data requested. If the data are not satisfactory, additional evidence must be produced by the company. Once the drug is registered, however, in many countries the burden of proof moves from the company to the registration authority. New in European Union legislation is that a marketing authorization is valid for a period of five years [10]. The authorization will be renewable for subsequent five years periods upon application by the company, accompanied by a dossier contain up-to-date information on pharmacovigilance in the form of periodic safety updates. It is not clear, however, if the European authority can demand the conduction of additional studies (e.g. for the testing of hypotheses regarding adverse reactions).

Differences between countries

Since the pioneering WHO Technical Reports [11], the principles of spontaneous reporting have been reviewed in several articles and books [6-8 12-17]. Somewhat different procedures have, however, developed in different countries [7 18] and different views exist with regard to important issues such as causality assessment [19], confidentiality, freedom of information, and reporting obligations. The Dutch Health Council has published a special report on 'Privacy in Postmarketing Surveillance', in which the need for anonymity of case reports is emphasized [20]. In the draft European Guideline on adverse reaction reporting, on the other hand, it is explicitly requested that case reports contain the surname and first names of the patients (although the provision 'if available and acceptable under national law' is added) [21]. New regulations in the European Union give companies and governments obligations with regard to the reporting of suspected adverse reactions [21-23]. In many countries in and outside the European Union reporting obligations do not exist, however, for physicians and pharmacists, i.e. those who actually observe patients with adverse reactions in practice. The number of countries, on the other hand, where adverse reactions reporting has become mandatory also to health care professionals is increasing.

In many countries (anonymised) data obtained through spontaneous reporting are publicly available under the freedom of information act (e.g. Australia, Canada, Nordic countries, USA). In other countries (e.g. France, Germany, UK), on the other hand, the data are confidential, in common with the registration file.

Problems

After approval of a drug also the study environment and scientific principles change. In PMS the users population and study parameters are not defined and fixed (as in a clinical trial) but, on the contrary, are unselected and open. PMS needs to be non-interventional, i.e. prescriber may not be influenced in their choice of a drug during data collection for PMS and a treatment may not be changed for the purpose of PMS. A characteristic feature of PMS is that, as compared with a clinical trial, often data on very large numbers of patients are needed (e.g. to detect rare adverse reactions). If two (or more) PMS activities take place simultaneously, the one may unwantedly influence or delay the other [24] and there may even be not enough patients in a country to assess all new drugs.

In PMS often problems are complex and questions difficult to solve. The available information often is associated with some uncertainty or is even inconclusive. Interpretation may be influenced by differences in opinion and background. Sometimes different conclusions may with good reason be attached to one and the same set of data.

Medicines are at the same time powerful health care instruments and profitable commercial products. The findings in PMS play a role in a complex environment encompassing many different and potentially conflicting interests [25] (e.g. commercial profit versus medical value, economical freedom versus health expenditure containment, company property versus freedom of information).

When evidence accumulates and knowledge increases a change in dose recommendation or indications for use may be needed, or additional safety measures may be required. The findings in PMS may impair the commercial value of a drug and in extreme situations lead to withdrawal. Even a false alarm may cause permanent damage to the drug.

In large countries, after approval the number of users of a new medicine may within a short period of time become very large. The higher the number of users of a drug is, the larger is its commercial value but also the possible number of victims of an unforeseen adverse reaction. Pharmacovigilance experts in drug companies in European countries are being given a personal responsibility in ensuring that data on adverse effects are promptly reported to the drug regulatory authority [21]. This responsibility should not be overruled by instructions in the company. Appropriate organisational arrangements in the company and strict employment contract provisions may be necessary to safeguard job security of pharmacovigilance officers.

The basic principle underlying the safe introduction of a new medicine is, that whenever a patient uses the drug he and his doctor and pharmacists must be prepared to (anonymously) participate in the national pharmacovigilance program. On the other hand, much importance is attached to the principle right of any patient to refuse the use of data originating from his or her medical history (except for insurance accounting purposes) [26]. Proposed new legislation in Europe regarding privacy and the confidentiality of personal health data is a real threat to future PMS [27]. My personal impression is, however, that modern patients think largely positively of postmarketing

drug evaluation and are well prepared to contribute, provided that commercial (and political) interests are excluded. Recent evidence is in support of this view [28]. It may be in the future that the public might demand effective and transparent surveillance of marketed drugs, in spite of current legislation regarding privacy, medical secrecy and drug regulation.

Good Practice

For reasons discussed above there is a need for Good Practice in PMS (GPP). Patients contributing data to PMS deserve a formal review of the protocol, with regard to appropriateness, relevance and ethics. GPP starts where GCP ends and should be a logical extension of the latter. Whereas GCP is predominantly concerned with the rights of individuals, GPP is primarily a matter of the public interest. The procedures in all activities in the field of PMS need to be as well-considered and clear as possible. In contrast to a clinical trial, in PMS it may be unusual (or impossible) to obtain informed consent of the individual patients. GPP may be the natural way of solving threatening incompatibilities between current legislation and regulation and the proper performance of PMS. Major points of interest in GPP are:

- Scientific principles (aims, methods, procedures, inclusion of patients).
- Ethics and legislation (responsibilities, rights and interests, privacy and medical secrecy).
- Accounting (protocols, standardization, reporting of study results).
- Review: approval of studies and systems (e.g. with regard to appropriateness, scientific efficiency and ethics), and inspection.
- Setting priorities and allocation of funds.

Current developments

Through the years the WHO Collaborating Centre for International Drug Monitoring has contributed much to the development and harmonisation of the methodology in spontaneous reporting [11 29-31]. In a few countries, e.g. France and Japan, recently national documents on pharmacovigilance have been prepared [32 33]. In addition, various bodies are contributing to the improvement of the procedures and regulations in this field. The Council for International Organizations of Medical Sciences (CIOMS), for example, has advised pharmaceutical companies on the international reporting of adverse reactions and the production of Drug Safety Updates [34 35] and is providing structured definitions of the WHO Critical Adverse Reaction Terms [36]. The Pharmacovigilance Working Party of the European Commission has drafted a number of Guidelines for marketing authorization holders, i.e. on adverse reactions reporting [37], periodic drug safety update reports [38], company sponsored postmarketing safety studies [39], and ongoing pharmacovigilance evaluation during the post-marketing period [40]. The new MEDDRA terminology for adverse drug reactions (Medical Dictionary for Drug Regulatory Affairs [41]) is under consideration for adoption in the global scheme of the WHO Collaborating Centre in Uppsala. Bénichou and co-workers have developed a series of structured etiologic-diagnostic assessment schemes for important or

frequent drug-induced disorders [42-43]. Although primarily focused on the pre-registration phase, parts of the work the Conference on International Harmonization (ICH) are also relevant to PMS [44]. The European Pharmacovigilance Research Group is working on a variety of mainly scientific issues in pharmacovigilance [45]. In the United Kingdom a code of behaviour in company-sponsored drug safety studies has been laid down in collaboration with the Medicines Control Agency in the Safety Assessment of Marketed Medicines SAMM Guidelines [46]. More recently, an excellent framework for conducting pharmacoepidemiologic studies has been developed by the International Society for Pharmacoepidemiology ISPE in the Guidelines for Good Epidemiology Practices for Drug, Device and Vaccine Research in the United States [33]. These and other activities are already anticipating GPP.

The next steps

For the further development of GPP, the following points need to be addressed:

1. To define the aims of PMS and to identify appropriate methods of data collection and assessment for the various aims and their specific advantages and limitations.
2. To design, standardise and describe in detail the methods and procedures for the collection, assessment and distribution of data (spontaneous reporting and other).
3. To identify the interests, rights and responsibilities of all parties involved: individuals (patients, doctors, pharmacists, investigators) and institutions (companies, governmental bodies, patients as a group).
4. To design protocols for the reporting (accounting) of data and findings, and to develop appropriate software for data processing.
5. To prepare a guideline for a data management code, specifying which data are available to whom, for which purpose, and under which conditions, and also referring to confidentiality.
6. To develop strategies for assessing quality and performance of PMS systems.
7. To establish an authoritative forum for the statistical review of pharmacoepidemiologic studies.
8. To audit in PMS.
9. To ensure professional autonomy (and job security) of pharmacovigilance officers.
10. To establish national 'Ethical PMS Committees' (or regional in large countries), for the coordination and review of the activities pertaining to points 1-9, especially with regard to:
 - appropriateness of protocols and procedures,
 - allocation of funds and setting priorities (with regard to study subjects),
 - enforcement of GPP rules,
 - protection of public health interest.

For spontaneous reporting systems the description in detail is needed of the appropriate procedures in the collection, processing, assessment and dissemination of data. The success of a spontaneous reporting system depends upon the quantity and quality of adverse reaction reporting, the organisation of the system, and the utilization of the collected data. With

regard to the level of reporting (input) the following criteria may be used:

- Reporting rate (e.g. number of case reports/10⁶ inhabitants/year).
- Reporting distribution, i.e. the percentage of physicians reporting and reporter characteristics (e.g. general practitioners, specialists, pharmacists).
- Reporting quality (e.g. according to the new WHO documentation grading [48]).
- Reporting efficiency (the proportion of relevant case reports, e.g. concerning unknown or serious reactions).

Drug utilization data are useful as a reference, e.g. while assessing reporting rates and differences or changes in reporting. Regarding the organisation of a pharmacovigilance centre it is of interest how the system for data acquisition is structured. The professional expertise of assessors and the mean assessment time per case report (or the number of staff members per 1000 case reports) may be used as parameters of the quality of data assessment at a centre. The budget available for pharmacovigilance and the sources and continuity of funding indirectly give information regarding organisational development.

The yearly numbers and the content of publications and changes in data sheets referring to spontaneous reporting, may be used as indicators of the utilisation of pharmacovigilance data (output). The frequency of data base searches is another possible parameter in this respect. Also a data management code can give information of data utilisation in a country.

Similarly, concrete and detailed guidelines are needed for all other activities in PMS. For the - national and international - establishment of GPP collaboration is needed from medical and pharmaceutical associations, academia, regulators and pharmaceutical companies. The support of authoritative institutions such as the World Health Organization may improve international harmonisation and acceptance. The public health interest in effective PMS is obvious. Since the necessary data have to come from the drug-using population at large, the willingness of individual patients to contribute is crucial. Patients are at the same time the source and the ultimate destination of information in PMS. Consumer and patient organisations should therefore also play a role in the development of GPP and the establishment of Ethical PMS Committees. As is always true in medicine, also in GPP the interest of the patients must come first.

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