TWENTY-SECOND WORLD HEALTH ASSEMBLY

Agenda item 2.2.3

PILOT RESEARCH PROJECT
FOR INTERNATIONAL DRUG MONITORING

Progress Report by the Director-General

1. In its resolution EB43.R17\(^1\) the Executive Board, emphasizing the importance of the pilot research project aimed at the establishment of an international system for monitoring adverse reactions to drugs, requested the Director-General to keep the Board and the Assembly informed of the progress of the project. Accordingly, the following report on the Pilot Research Project for International Drug Monitoring (IR 0531) has been prepared.

Background

2. In resolution WHA18.42 the World Health Assembly requested the Director-General "to study further the requirements of an international programme for the collection, analysis and dissemination to Member States of information on adverse drug reactions". Following the recommendation by a WHO Scientific Group,\(^2\) the World Health Assembly in resolutions WHA19.35\(^3\) and WHA20.51\(^4\) requested that a pilot research project for the establishment of an international system of monitoring adverse reactions to drugs should be carried out utilizing funds provided by the Government of the United States for this purpose.

3. The primary objective of monitoring drugs for adverse reactions is to define at the earliest possible time the capacity of a drug to produce undesirable effects. The following outline of the nature and operation of such monitoring was prepared by a WHO Scientific Group on Monitoring Adverse Drug Reactions\(^2\) and was circulated to all Member States.\(^5\)

"The full hazard of a drug is sometimes not revealed before widespread clinical use. For example, various factors, such as differences in metabolism among different species, may lead to erroneous conclusions from animal experiments. Controlled clinical trials, even when carried out on a large scale, may fail to reveal serious adverse effects if such effects occur infrequently, or if the population involved in such trials differs substantially from the general population with respect to such factors as age, sex, race, pregnancy and previous exposure to the drug. In addition, between animal experiments and early clinical trials, and again between clinical trials and general marketing, a drug may be modified with respect to specifications, method of manufacture, excipients, and possible impurities. Systematic monitoring is the only method of achieving any

\(^{1}\) Handbook of Resolutions and Decisions. 10th ed., p. 114.


\(^{3}\) Handbook of Resolutions and Decisions, 10th ed., p. 112-113.

\(^{4}\) Handbook of Resolutions and Decisions, 10th ed., p. 113

objective assessment of the hazards associated with a drug after it appears on the market."

Concurrently, a number of Member States were in the process of developing national drug monitoring systems to receive and evaluate reports of adverse drug reactions from doctors both in practice and in hospitals.

4. Resulting from the reports of several scientific groups,\(^1\) it was decided that, during its pilot stage, the WHO drug monitoring programme should

(a) assess the feasibility or otherwise of an international system of drug monitoring;

(b) develop the methodology for recording case histories of adverse reactions to drugs, systems for analysis and feed-back of data to national monitoring centres;

(c) undertake analysis of instored data on an experimental basis;

(d) provide facilities for searches by WHO staff and national centres on the types and patterns of adverse reactions to individual drugs; and

(e) make a preliminary study of the contribution of drug monitoring to research in pharmacology and therapeutics.

5. For participating national centres the following criteria as recommended by the Scientific Group on International Drug Monitoring in 1965\(^2\) were adopted:

(a) a designated national mechanism or system responsible for monitoring and obtaining reliable data on adverse drug reactions;

(b) continuity of staff and services for collecting, verifying and storing reports of adverse reactions;

(c) a national standard for terminology and identification of drugs;

(d) agreement to provide reasonably uniform data to WHO;

(e) facilities and ability for examining the validity of reports, and for detailed study, when necessary, of reported adverse reactions; and

(f) availability of data on drugs used nationally, and the ability to estimate the extent of drug usage.

6. Ten countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Republic of Ireland, Netherlands, New Zealand, Sweden, United Kingdom and United States of America) with established drug monitoring systems agreed to participate by forwarding case reports of adverse reactions received in their national centres to the WHO Pilot Project Centre located in Alexandria, Virginia, USA. Between March 1968 and May 1969, the latter has received 11 268 case reports on adverse reactions.

7. Regular consultations have taken place between the national centres and the WHO Centre. In 1968 special meetings were held to co-ordinate linkages at the national and international levels. Experts from national centres have expressed appreciation of the value to their centres in being associated with the project, especially in connexion with terminology, classification,


recording and analytical procedures. Uniformity in those matters will facilitate the handling of data, especially as the number of reports available to the WHO Centre is expected to increase to several thousands per month in the near future.

**WHO Centre developments**

8. The WHO Centre has prepared an agreed terminology and classification for adverse reactions suitable to the requirements of the ten national centres and has developed basic methods for computer recording and analysis of the reports. The compilation of a "drug name dictionary" to record the drugs involved - sometimes eight or ten in a single report - required separate pharmacological, therapeutic and chemical classifications for drugs. It has been considered essential that the computer programme should enable reactions to be studied from several points of view, for example, on the basis of their chemical, pharmacological or therapeutic features. The WHO Centre has been faced with the task of developing separate and complete classifications to describe drugs under those categories.

9. After completion of the working classifications a large proportion of reports received has been coded according to the computer programme, with due attention to the need of establishing links between the relevant aspects of the data. A careful study was made on how to prepare the summary reports to be printed by the computer so that they will meet the essential needs of the national centres. For the purpose of developing the most useful design types for feed-back of data to national centres, specimens were made available to these centres. Suitable statistical techniques were explored so that the most meaningful assessment could be obtained from the heterogeneous data available. Methods to detect new reactions as well as increases in levels of well known reactions are being developed. Even at this early stage well known patterns of "drug and reaction" associations were evident from outprints of recorded data.

**Co-operation with other WHO programmes**

10. The Pharmaceutical unit has provided International Non-proprietary Names which are employed as an integral part of the drug recording system. The International Classification of Diseases (ICD) is being used for the recording of the indications of drug treatment as well as those adverse reactions which are themselves listed as specific disease entities in the ICD. The terminology for adverse reactions and the drug classifications as they are developed in the pilot project may be useful for future ICD amendments. The Division of Epidemiology and Communications Science has provided advice on statistical and epidemiological problems. The Data Processing unit has given valuable assistance in the development of the computer programme.

11. It is anticipated that these and other services of WHO will eventually derive benefit from their association with the drug monitoring programme. For example, outprints of certain types of adverse reactions such as foetal malformations and drug dependence will be available to responsible units of WHO as well as the national monitoring centres for study.

12. The essential needs of the project for premises, equipment and data processing have been provided by the Government of the United States under a grant which expires in May 1970. In accordance with resolution WHA20.51 the Director-General will further report on the results of the pilot project for the international monitoring of adverse reactions to drugs.