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TWENTY-THIRD WORLD HEALTH ASSEMBLY

Agenda item 2.11

WHO PILOT RESEARCH PROJECT FOR INTERNATIONAL DRUG MONITORING

Report by the Director-General

The following correction should be made to this document:

Page 19, para. 58 The amount in the "Geneva" column against item 3 of the table should read "US$ 76 152" instead of "US$ 77 152".

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WHO PILOT RESEARCH PROJECT FOR INTERNATIONAL DRUG MONITORING

Report by the Director-General

CONTENTS

SUMMARY

(i) The World Health Assembly in resolutions WHA19.35[1] and WHA20.51[2] requested the Director-General to initiate a pilot research project with the aim of establishing an international system of monitoring adverse reactions to drugs on the basis of information derived from national centres utilizing funds provided to that effect by the Government of the United States of America.

(ii) The primary objective of drug monitoring for adverse reactions is to identify at the earliest possible moment the liability of a drug to produce undesirable effects which were not detected during its clinical trials. As adverse reactions to drugs may occur in all countries and their early detection requires a reporting system covering large populations, there is an obvious need for international co-operation in that field.

(iii) The aim of the WHO pilot project has been to investigate the feasibility of an international drug monitoring system based on case reports of adverse reactions to drugs recorded in national centres. The WHO pilot project was based on a WHO drug monitoring centre, located in Alexandria, Virginia, the United States of America. Ten countries which possess established centres have agreed to participate in the project. From the beginning of the operation of the WHO centre in February 1968 until December 1969, over 24 000 case reports were received from the national centres.

(iv) The WHO centre has developed systems for processing, recording, storing, linking and retrieving data provided in the case reports. It has established classifications for drugs and terminologies for recording adverse reactions. Computer print-outs have been forwarded to the participating centres with the following types of information: (a) frequency of reactions recorded for each drug; (b) frequency of reports on drugs associated with an adverse reaction, including cumulative totals for various periods; (c) condensed data for rapid reference; and (d) drug reference lists. Particular efforts have been made towards developing signalling programmes to increase the effectiveness of the system as an early warning device.

(v) The project has been kept under continuous review throughout the pilot phase. A detailed analysis of the results obtained was carried out in September 1969 by a meeting including representatives of the participating national centres. A meeting of consultants in November 1969 was called upon to assess the results achieved and to make recommendations as to the possibility and desirability or otherwise of further developing the activities initiated under the project.

(vi) As a result of these reviews and consultations, the conclusion was reached that the WHO pilot project had satisfactorily fulfilled the tasks assigned to it and that on the evidence provided a system of international monitoring of adverse reactions to drugs was feasible.

(vii) The evaluation of the project further demonstrated that such an international drug monitoring programme could yield substantial benefits in related fields of medicine and public health, e.g. drug safety control, drug dependence, clinical pharmacology and therapeutics, congenital malformations and human genetics, international classification of diseases, etc., as well as for the development of monitoring methodology. Such benefits would not be limited to the countries directly associated with the programme but would extend to non-participating countries as well.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 112-113.

[2] Handbook of Resolutions and Decisions, 10th ed., p. 113.

(viii) The project could now move into a primary operational phase with the objective of adjusting the methodology evolved during the pilot phase to a system of an operational character. A comprehensive programme assessment should be undertaken preferably no later than three years after the start of the primary operational phase, to lay down the basis for the development of a fully-operational system.

(ix) The Executive Board at its forty-fifth session considered a progress report by the Director-General and, noting the positive results obtained, recommended that the project be so developed as an integral part of the programme of the Organization.[1]

(x) A cost-effectiveness study of the project was carried out to evolve a detailed work plan for the primary operational phase and determine its requirements and related costs, taking into consideration the alternative location of the project in Alexandria, Virginia, United States of America, as at present, or at WHO headquarters in Geneva. As a result of the study, it was concluded that from the management point of view the system developed during the pilot phase for processing, recording and retrieving data relating to adverse reactions to drugs was sound. It was further found that the location of the project in Geneva would be less costly than its location in Alexandria, United States of America. It is worth noting in this connexion that the computer aspects of the project have been developed in such a way as to be compatible with the computer facilities available at WHO headquarters.

(xi) On the basis of the above, the budgetary requirements of the proposed primary operational phase have been determined for 1970, 1971 and 1972. Ways and means of financing the project have been studied and alternative solutions are submitted to the Health Assembly for its consideration and decision.

(xii) The Director-General wishes to acknowledge the co-operation shown by the Government of the United States of America, and the determinant support it has given to the pilot phase, as well as the most valuable contribution of the national centres both in the United States of America and in the nine other countries participating in the project.

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[1] Off. Rec. Wld Hlth Org., 181, resolution EB45.R26.

I. INTRODUCTION

Background

1. The Twentieth World Health Assembly, having considered a report of the Director-General on International Monitoring of Adverse Reactions to Drugs, adopted resolution WHA20.51[1] in which, inter alia, it requested the Director-General to take the necessary measures to carry out a pilot research project on the modalities of an international system of monitoring adverse reactions to drugs, under a grant from the Government of the United States of America and to report on its results to the World Health Assembly. The Director-General accordingly submits the following report on the Pilot Research Project for International Monitoring of Adverse Reactions to Drugs.

2. Previous reports on the subject to the Eighteenth World Health Assembly, which adopted resolution WHA18.42,[2] and to the Nineteenth World Health Assembly, which adopted resolution WHA19.35,[3] appraised the requirements of an international programme for the collection, analysis and dissemination of information on adverse drug reactions and proposed guidelines for its development.[4] The present report is primarily aimed at recording and assessing the results of the pilot project; but it will, in addition, indicate further requirements of the programme if it is developed into full operation, including related cost estimates.

3. At its forty-fifth session, the Executive Board, after detailed consideration of a progress report by the Director-General, adopted resolution EB45.R26.[5] The Board noted the positive results attained by the project and recommended to the Twenty-third World Health Assembly that it be further developed to become operational as an integral part of the programme of the Organization.

The purpose of drug monitoring

4. The rapid growth of drug therapy is widely recognized as having produced great benefits to the health of the community. Less widely realized is the extent to which this has been accompanied by an increase in adverse reactions to drugs, quite often trivial but an appreciable proportion of which are sufficiently serious to offset part of the benefits. Eight years ago, the thalidomide tragedy drew the attention of health authorities and of the general public to this problem and its implications. The use of potent drugs inevitably carries the risk of drug-induced illness, and possibly death, as illustrated by the following quotation:

> "Perhaps some 5% of the beds in our general hospitals are occupied by patients suffering to a greater or less extent from our efforts to treat them. Yet the incidence of adverse reactions to drugs is not well known and even major reactions often go unrecognized. Indeed one of the urgent tasks confronting us today is to put such reactions on a sound epidemiological basis. Thus their collection, tabulation, and analysis on a national and ultimately on an international scale are of great importance."[6]

It follows that medical treatment with any drug demands a knowledge of its adverse effects as well as of its therapeutic effectiveness. Incomplete knowledge of the kind, severity and frequency of adverse effects to drugs is a major weakness of therapeutic practice and appreciation of this fact has led to the establishment in a number of countries of systems of monitoring drugs for suspected adverse reactions.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 113.

[2] Handbook of Resolutions and Decisions, 10th ed., p. 112.

[3] Handbook of Resolutions and Decisions, 10th ed., pp. 112-113.

[4] Off. Rec. Wld Hlth Org., 148, Annex 11.

[5] Off. Rec. Wld Hlth Org., 181, p. 17.

[6] Dunlop, Sir Derrick (1969) Brit. med. J., 2, 622.

5. The primary objective of drug monitoring for adverse reactions is to identify at the earliest possible moment the liability of a drug to produce undesirable effects which were not detected during its clinical trials. As has been pointed out by a WHO Scientific Group on Drug Monitoring, and again emphasized by the Scientific Group on the Clinical Evaluation of Drugs,[1] many adverse effects of drugs in man are not predictable by experiments on animals or controlled clinical trials. A systematic follow-up of drugs after their introduction into general use is therefore essential.

6. As the problem of adverse reactions to drugs exists in all countries and the early detection of some serious adverse reactions requires reports to be obtained from large populations, the need for international co-operation soon became obvious. The report of the Director-General to the Executive Board at its thirty-seventh session[2] provided guidelines for the development of an international project.

Definitions

7. For the purpose of the project the following definitions have been adopted:

A drug is defined as any substance administered to man for the prophylaxis, diagnosis or therapy of disease, or for the modification of a physiological function.

An adverse reaction to a drug is defined as one which is noxious, unintended and occurs at doses normally used in man.

Drug monitoring is defined as the systematic reporting, recording and evaluation of adverse reactions to drugs available with or without prescription. Information on adverse reactions can be obtained either through voluntary reporting to designated centres by practising doctors and hospitals (spontaneous monitoring), or by epidemiological techniques aimed at systematic coverage of representative samples of the patient or of the physician population (intensive monitoring).[3]

The WHO Pilot Project consists of a feasibility study of the modalities of an international system for monitoring adverse reactions to drugs. It is composed of the WHO Drug Monitoring Centre and the participating National Drug Monitoring Centres.

The WHO Drug Monitoring Centre is the pilot centre at present located in Alexandria, Virginia, United States of America, responsible for the development of the project, on the basis of a two-way flow of information on adverse reactions to drugs, in relation with national centres.

A National Drug Monitoring Centre is an agency, usually governmental, charged with the responsibility of monitoring adverse reactions to drugs on a country basis.

II. THE WHO PILOT PROJECT

Objectives and procedures

8. The aim of the project has been to investigate the feasibility of an international drug monitoring system based on case reports of adverse reactions to drugs recorded in national centres according to the following objectives:

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[1] Wld Hlth Org. techn. Rep. Ser. (1968) 403.

[2] Off. Rec. Wld Hlth Org., 148, Annex 11.

[3] Wld Hlth Org. techn. Rep. Ser. (1969) 425.

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

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

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

(d) to study the possible contributions of drug monitoring to pharmacology and therapeutics.

The functions and procedures deemed necessary for the achievement of the objectives of the project are shown in the chart in Fig. 1.

Participating national monitoring centres

9. Data essential to the development of the project have been provided by 10 countries (Australia, Canada, Czechoslovakia, the Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, the United Kingdom of Great Britain and Northern Ireland and the United States of America which have established national drug monitoring centres and have agreed to participate by forwarding to the WHO Centre case reports of adverse reactions to drugs.

10. For participating national centres, the following criteria, as recommended by the WHO Scientific Group on International Drug Monitoring in 1965, were adopted:

(a) a designated national organ responsible for monitoring data on suspected adverse drug reactions;

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

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

(d) availability of data on, and terminology for identification of, drugs used nationally, and the ability to estimate the extent of drug usage.

11. National monitoring systems depend upon the reporting by physicians of cases of suspected adverse reactions to drugs to a national monitoring centre. After careful validation of the data, analyses and further investigations are carried out to confirm or refute the association between a drug and a suspected reaction. The methods adopted by any national centre for this purpose depend upon conditions within the country and vary according to the drug, the reaction and the population at risk.

12. Predictably a wide range of variability in submitted data exists, due to differences in history taking, examination and investigations on the one hand, and to available recording facilities and staff on the other. The WHO Centre has encouraged the acquisition of data from all available sources, such as general practitioner, specialist, hospital. In order to ensure a desirable level of uniformity in the presentation of case reports, the recommendations of a WHO Scientific Group held in Geneva in November 1965 that there should be a basic or minimum content of data were adopted by the participating national centres. The required content and form of presentation of case reports are described in a "Guide to Participating Countries" and in the "WHO Drug Reaction Report Form".

13. From the beginning of the operation of the WHO Centre in February 1968 until December 1969, 24 085 case reports were received from national centres (see Fig. 2) and have provided suitable material for methodological studies.

FIG. 1

WHO PILOT RESEARCH PROJECT FOR INTERNATIONAL DRUG MONITORING EVENT AND PROGRESS CHART NO. 1 DMQ/RDM

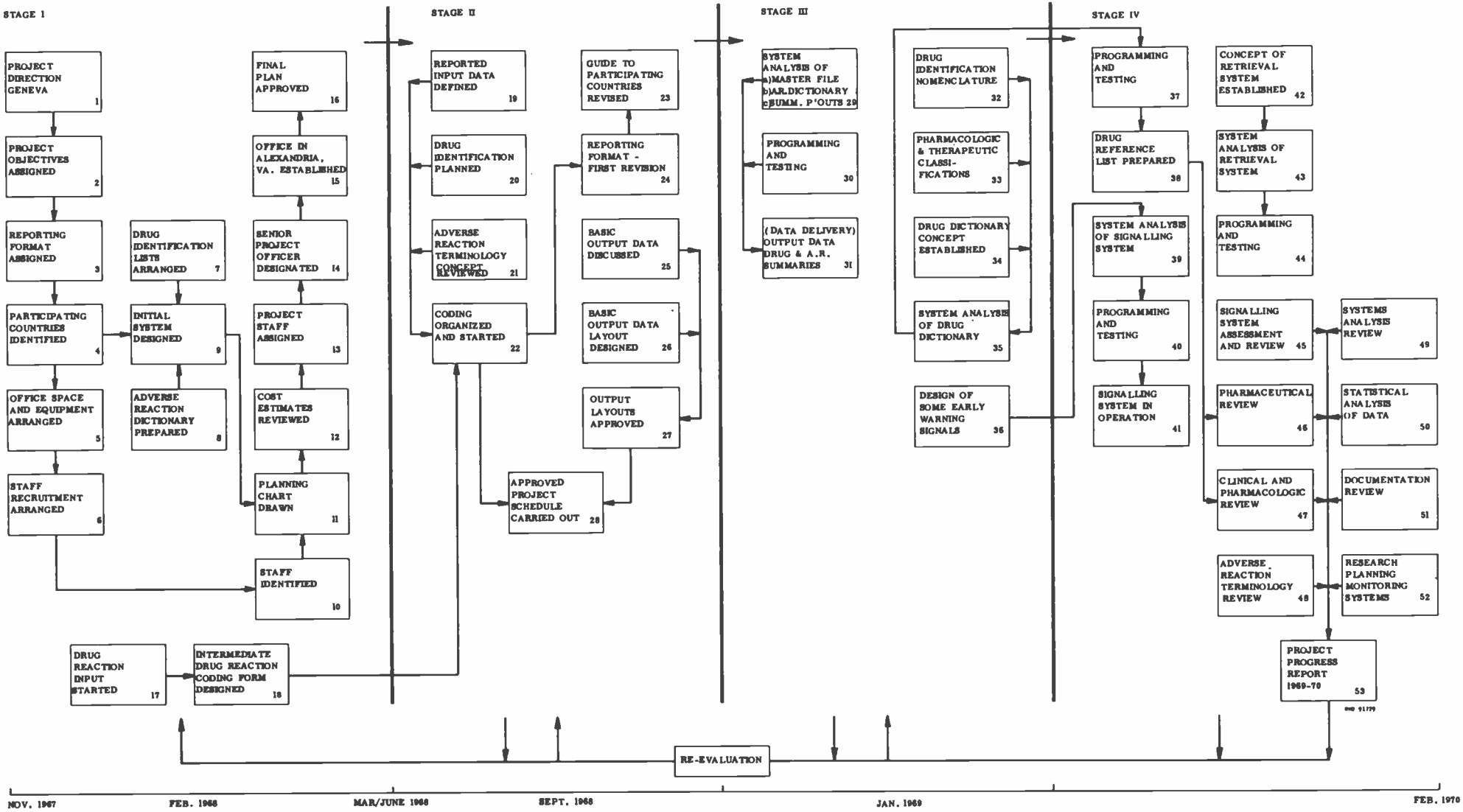


FIG. 2. REPORTS RECEIVED IN THE WHO DRUG MONITORING CENTRE, MARCH 1968 - DECEMBER 1969

Dates	Australia	Canada	Czeckoslovakia	Federal Republic of Germany	Ireland	Netherlands	New Zealand	Sweden	United Kingdom of Great Britain and Northern Ireland	The United States of America	Total	
											No.	Cummulative
1968												
March	-	-	-	31	17	-	28	51	-	-	127	127
April	-	-	19	18	7	-	-	41	-	229	314	441
May	59	267	13	16	17	-	39	47	56	183	697	1 138
June	-	169	-	18	13	95	46	36	184	64	625	1 763
July	135	183	-	21	-	-	38	163	335	91	966	2 729
August	-	131	10	29	-	-	38	44	314	-	566	3 295
September	45	158	-	32	22	99	-	54	134	-	544	3 839
October	58	127	-	-	-	21	21	93	399	-	719	4 558
November	36	146	-	44	18	-	30	68	-	-	342	4 900
December	49	-	-	44	10	-	31	48	478	85	745	5 645
	382	1 181	42	253	104	215	271	645	1 900	652	5 645	-
1969												
January	42	257	25	27	-	196	30	74	404	69	1 124	6 769
February	-	156	-	46	16	201	131	31	236	239	1 056	7 825
March	-	149	-	-	-	245	24	-	397	-	815	8 640
April	64	244	-	57	-	-	-	127	366	776	1 634	10 274
May	98	166	-	68	-	-	-	111	404	187	1 034	11 308
June	-	213	-	102	50	150	50	235	319	12	1 131	12 439
July	-	277	-	81	22	-	-	105	148	1 435	2 068	14 507
August	141	226	-	51	9	-	45	165	696	580	1 913	16 420
September	76	-	28	61	15	399	-	87	175	967	1 808	18 228
October	153	323	-	-	-	250	55	145	-	1 658	2 584	20 812
November	85	-	-	71	31	-	50	89	317	1 794	2 437	23 249
December	-	-	14	60	-	-	50	104	350	258	836	24 085
	659	2 011	67	624	143	1 441	435	1 273	3 812	7 975	18 440	-
1968 + 1969	1 041	3 192	109	877	247	1 656	706	1 918	5 712	8 627	24 085	-
Adverse reaction reports per 1000 hospital beds	7.7	15.0	.8	1.4	6.3	18.2	25.4	18.1	12.2	5.1	6.8	-
Adverse reaction reports per 100 physicians	66.1	133.0	4.1	9.5	83.7	115.3	220.6	225.1	103.8	31.1	46.3	-
Adverse reaction reports per 10^6 population	90.2	159.2	7.6	15.2	85.6	133.0	263.8	245.6	104.3	43.8	63.2	-

14. In order to accomplish the primary objective, i.e. an early signalling system, the time lapse between the occurrence of an adverse reaction and its evaluation should be minimal. Various factors either separately or in combination could contribute to a time lapse between:

(a) onset of the reaction and its observation by the patient and/or doctor;

(b) observation of the reaction and reporting to the national centre;

(c) receipt of the report at the national centre and processing in the national centre;

(d) despatch from the national centre and receipt at the WHO Centre; and

(e) receipt at the WHO Centre, computer recording and printout distribution.

A detailed study of the time factors has been undertaken in order to achieve a minimal processing time for data received.

The activities of the WHO Drug Monitoring Centre

15. The WHO Centre was established in January 1968 in Alexandria, Virginia, United States of America, utilizing premises and computer facilities provided under a grant from the Government of the United States of America. Case reports of adverse reactions recorded in the participating national centres have been received regularly since March 1968. Systems for processing, recording, storing, linking and retrieving reports have been developed. Computer printouts containing recorded data in various forms have been forwarded to national centres.

Coding and data processing

16. (a) Drug reaction reports from participating national centres are date stamped, arranged by country and country serial number, and filed, pending coding.

(b) Data from the reports are transcribed onto a WHO data coding form. When coding takes place, a WHO record number is given to each coding form uniquely identifying the report and its origin.

(c) Once a report has been coded, it is then checked by the medical section for medical description, clinical assessment and research area coding.

(d) The document set is then passed on to a second section for drug data and pharmaceutical checking.

(e) When this stage has been completed, the reports and coding forms are despatched weekly to the computer for keypunching. The forms are verified to make sure that at least one coding form has been completed for each report.

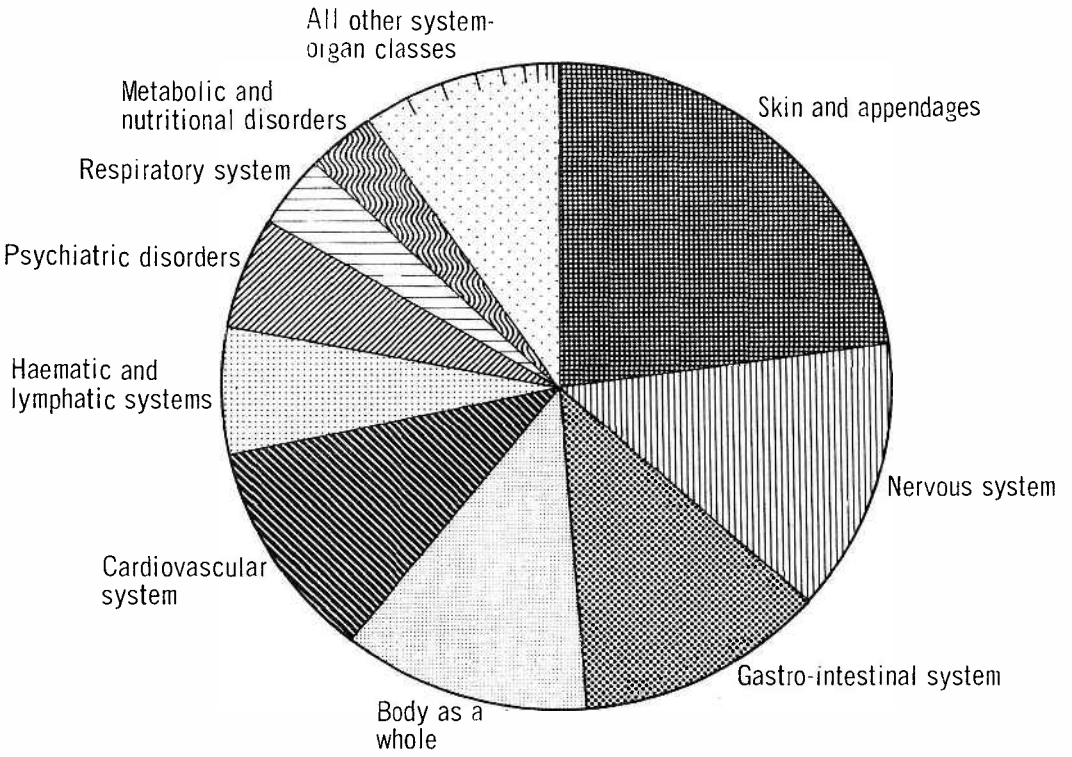
(f) Reports that present any ambiguity or difficulties are recorded in an internal "review" file, by country, and consultations are held on a regular basis to elucidate the problem or to decide whether to request additional information from the national centre.

Adverse reactions classification and terminology

17. It is the aim of the WHO Centre to use as few preferred adverse reaction terms as possible as descriptors in the transcription of the adverse reaction from national centre reports. The list of preferred adverse reaction terms is an open-ended document with scope for modification in order to reduce or expand the number of working terms where desirable. To date, 534 adverse reaction descriptors have been used. These preferred terms are grouped according to a system-organ classification. The frequency with which they occur in the reports processed is shown in Fig. 3.

FIG. 3

SYSTEM-ORGAN CLASS DISTRIBUTION OF ADVERSE REACTIONS REPORTED*
MARCH 1968 - DECEMBER 1969



* based on 13 187 drug reactions reported in 6 170 reports tabulated.

In February 1970 a revised list of adverse reaction preferred terms was distributed to the national centres. The new list is based on a two-tier system of adverse reaction recording in order to group closely related reactions under the same term, e.g. ABORTION, whether complete, missed or threatened, to be included under ABORTION. In addition, some reduction in the number of preferred terms is being investigated, e.g. SPASTIC PARALYSIS, MONOPLEGIA and HEMIPLEGIA to include spastic paresis, monoparesis and hemiparesis, respectively.

18. The most complete description of reported adverse reaction available is desirable from national centres. This provides for more accuracy in transcription to preferred terms, more complete evaluation, and better material for research purposes. The information already submitted has provided descriptions of adverse reactions in sufficient detail to allow studies to be carried out on coding methods by which the possible mechanisms, causal relationships and severity of reactions might be identified.

Drug terminology

19. In their reports national centres record drugs, in the following order of preference:

trade or proprietary name
international non-proprietary name
national non-proprietary name
chemical name (structural formula)

Before a drug trade name is transferred from a drug reaction report to the coding form, the official or selected drug list of the particular country is consulted for verification of the drug and standard spelling according to the list. This procedure is followed in every case to facilitate recording compatibility between the WHO Centre and the national centre. As an example, hyphens and periods are entered when the drug list so indicates.

20. For non-proprietary names, two preferred sources are used – the International Non-proprietary Names (INN) and the International Pharmacopoeia (IPH). However, this does not preclude the national centres from reporting a nationally approved name which is thus entered on the coding form and stored in the master file. It is then printed in the WHO Centre Drug Reference List, cross-reference being made to the corresponding INN name.

21. The "Drug Reference List" contains any drugs reported in association with adverse reactions. This List serves as an alphabetic cross reference for trade, proprietary and non-proprietary drug names, with those containing the same active ingredients grouped together. In order to deal with the problem of recording drugs of various origins and composition, seven designations are used for classifying the type of drug name, as follows:

N = non-proprietary name; T = trade or proprietary, single compound; M = mixture (multiple compound drug) and trade or propreitary name; X = mixture (multiple compound drug) and non-proprietary name (APC); C = component in multiple compounded drug; K = chemical name; R = code number or code designation.

22. In maintaining the original drug nomenclature for each country, the Drug Reference List compiled by the computer is a useful reference for each participating national centre to identify a drug which might be used in another country under a different name.

Classifications for drug recording

23. Separate therapeutic and pharmacological classifications have been developed for drug recording in the WHO Centre. The purpose of using a pharmacological as well as a therapeutic classification is to achieve more informative linkages of drug groups with adverse reactions. Before a drug is assigned to a pharmacological class, authoritative references are consulted. There is computer provision for a total of six therapeutic and six pharmacological classes for each drug.

24. The development of an internationally acceptable drug and adverse reactions terminology and classification is under study with the WHO Health Statistics Division with the aim of their eventual inclusion in the International Classification of Diseases.

Output data presentation

25. From the early stages of the project, consideration has been given to forward planning of the output so that the participating centres could make the most of the accumulated data. The following documents illustrating the recording methodology developed by the WHO Centre have been forwarded to national centres since February 1968:

WHO Centre Adverse Reaction Preferred Terms		Despatched	Feb. 1968
Modified Alphabetical Version		"	Jan. 1969
		"	Feb. 1970
WHO Centre Adverse Reaction Preferred Terms		"	Feb. 1968
System-Organ Class. Version		"	Jan. 1969
		"	Feb. 1970
Therapeutic Classification of Drugs	1st Edition	"	Jan. 1969
	2nd Edition	"	July 1969
	3rd Edition	"	Jan. 1970

Pharmacological Classification of Drugs	1st Edition	"	Jan. 1969
	2nd Edition	"	July 1969
	3rd Edition	"	Jan. 1970

26. The initial computer programming system has enabled summarized data on adverse reactions to drugs to be sent to national centres at regular intervals commencing in March 1969. Based on the constructive reviews received from the national centres, the presentation of data was subsequently improved.

(i) Reference reports

These documents contain summarized voluminous information on all drugs and adverse reactions reported to the system.

Report Type A is drug-oriented and contains information on all reported drugs and adverse reactions, divided into three different time periods and sub-grouped into suspected and other categories. The information is sorted by drug-name, system-organ classification and adverse reaction. The drug-name can be the reported name, or grouped under its preferred name.

Report Type B is complementary to Report Type A and is adverse reaction-oriented. It contains information on all reported drugs and adverse reactions, divided into three different time periods with sub-grouping into suspected and other categories. The information is sorted by system-organ classification, adverse reaction and drug name. The drug name can be the reported name or grouped under the preferred name.

Report Type C contains summarized data based on Report Type A.

27. (ii) Scanning reports

These reports are essentially similar to the above but in a more concise form and include additional information.

Report Type D contains information on drugs suspected of being causally related to an adverse reaction, the degree of severity of the reaction, the sex and age-group of the affected patients.

Report Type E contains information on drugs reported in relation to adverse reactions during three different time periods. The number of fatal reactions recorded to specific drugs is also included.

Report Type F contains information on reported drugs listed by country. The information can be grouped and printed in a number of ways (maximum 54 ways) e.g. by Pharmacologic Classification, Therapeutic Classification, Preferred Name, Reported Name, and Ingredient for Multiple Ingredient Drug, etc. The document also contains information on the total number of reports, the total number of adverse reactions, and frequency of affected system-organ group, on a country basis.

28. (iii) Signalling reports

A large part of the computer effort has been devoted to the development of a variety of signalling programmes in order to increase the effectiveness of the project as an early warning device.

This type of report is generated automatically by the computer whenever the stored data reveal changes in reporting outside certain specified limits. At present, programmes are in operation to signal:

"New to the system" - to detect drugs, adverse reactions, and drug-adverse reaction associations newly reported. Whenever, during the updating of the master file, the computer detects any of the above, a signal printout becomes available. At present, many well-known drug-adverse reaction combinations are new to the system because of the relatively small files but as project files are built up, this signal will gain in objective value.

"Increased rate of reporting" - to detect a "significant" increase in reporting of a drug, an adverse reaction or a drug-adverse reaction combination. Then the level of reporting on a drug, expressed as a ratio of the number of reports on a drug to the total number of drugs reported for a given time period (or batch of reports), differs significantly from the preceding ratio calculated for another period of time (or batch of reports), a signal is generated by the computer. Similar programmes are developed to signal when a particular adverse reaction is increasingly reported or when the number of reports of a particular drug and adverse reaction combination increased significantly from one period of time to another.

Special search format and procedure

29. The WHO Centre is now in a position to produce additional reports in answer to Special Search requirements so that data additional to that already stored in the computer files be made available to national centres. These search facilities to meet specific enquiries from national centres could be developed in the early stages of the operational phase of the project.

Computer system development

30. To meet the objectives of the project, approximately 110 computer programmes have been designed; of these, 68 are used for file maintenance and production of external reports, the remaining programmes being used internally in the WHO Centre. The system provides for the inclusion of reports from new participating countries when desired.

Project assessment

31. All the technical aspects of the project described above have been kept under continuous review throughout the pilot phase by the project staff and by the officers concerned at WHO headquarters, with the help of consultants for specific aspects of project development.

A meeting of representatives of the participating national centres, with the staff of the WHO Centre, was convened in September 1969 to carry out a detailed analysis of the project.

A meeting of consultants in November 1969 was called upon to assess the results achieved and to make recommendations as to the possibility and desirability, or otherwise, of further developing the activities initiated under the pilot project.

32. As a result of these reviews and consultations, the conclusion was reached that the WHO pilot project had satisfactorily fulfilled the tasks assigned to it and that, on the evidence provided, a system of international monitoring of adverse reactions to drugs was feasible. This conclusion led to practical proposals as to the possibility of setting up an operational international system for monitoring adverse reactions to drugs.

The progress achieved in specific aspects of the pilot project was noted by the meeting of consultants which acknowledged the satisfactory results obtained in the development of systems for processing, recording, storing, linking and retrieving reports as well as for the validation and evaluation of data. Prepared dictionaries of preferred terms for drugs and adverse reactions, it was found, were already of considerable assistance to the participating drug monitoring centres.

III. POTENTIAL BENEFITS OF INTERNATIONAL DRUG MONITORING

33. Valuable contributions to health programmes in a number of areas could accrue from an international drug monitoring system.

Drug safety control

34. An international drug monitoring programme with rapid accumulation and dissemination of information on adverse drug reactions could greatly augment and complement the work of the national drug monitoring centres. It could be of particular benefit to national centres receiving relatively small numbers of reports, which could draw on the data available from the International Centre to supplement their own information.

35. Situations may arise in which reports of an adverse reaction to a drug occurring in different countries could be appreciated adequately only when collated at the International Centre. In addition, collated reports, especially those involving new drugs released for marketing, would be of considerable value to both the countries in which the drug is available and those in which it has not yet been released. Should the International Centre find unequivocal evidence of a serious drug hazard, all countries should be informed without delay, thus enabling them to take the necessary action.

36. Non-participating countries are also likely to receive substantial benefits from an international monitoring system:

(a) Such a system would raise the standards of safety in the choice of drugs available on the world market and in their methods of administration. All countries stand to gain by the earliest possible recognition of hazards encountered in countries which initially use a new drug.

(b) Information on drug reactions can be expected to lead to improved evaluation of drug safety in countries with national monitoring systems. Information on decisions taken subsequent to such evaluation would be brought to the knowledge of non-participating countries as is the practice already under resolution WHA16.36[1] which requests Member States to communicate to WHO decisions to prohibit or limit the availability of a drug causing a serious adverse reaction.

37. An international programme could provide valuable advice and assistance for the establishment of new national centres. The training of specialist staff and exchange of ideas and experience for the development of further techniques for drug monitoring could be promoted.

Clinical pharmacology

38. Drug monitoring could produce evidence of a cause and effect relationship between a drug and an adverse reaction, give the clinical pharmacologist leads for the elucidation of the mechanisms of adverse reactions and orientate the clinician towards more rational bases for therapeutics and a safer use of drugs.

Drug dependence

39. Drug dependence is recognized as a serious adverse reaction to a number of drugs including those used therapeutically. Relevant case reports, particularly those associated with new drugs, would be of interest to national as well as to international organs concerned with drug abuse and its control.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 111.

Congenital malformations and human genetics

40. The association between the administration of certain drugs during pregnancy and congenital malformations has been intensively studied. However, the relationship of drugs to several of the more commonly occurring malformations, e.g. cleft palate, has not been fully determined. There is evidence that genetic material in germ cells may be changed by exogenous influences, including drugs. Reports of abnormalities compiled in drug monitoring centres and in registries of congenital malformations should be linked for the study of possible relationships between drugs and malformations. Certain adverse reactions, such as those occurring within ethnic groups or suspected of being caused by anomalies of drug metabolisms, would be of interest in the field of human genetics.

Monitoring methodologies in other fields

41. The development of a sound international programme for drug monitoring can be of considerable methodological value to surveillance programmes in other fields of public health. Monitoring techniques of a similar character will be required to assist in elucidating health problems where planned experimentation is not feasible and observational techniques only are available, to provide systematic inferences on likely chains of causation within a population, e.g. factors such as genetic and somatic, environmental contaminants (pesticides, exhaust fumes, industrial wastes, radioactive elements), infectious agents (e.g. viruses) and as yet unknown deleterious substances.[1]

International Classification of Diseases

42. Terms and classifications for recording the adverse effects of drugs developed on an international scale could provide the basis of terminologies for revised editions of the International Classification of Diseases.

IV. PROPOSALS FOR FUTURE DEVELOPMENT

43. On the basis of the conclusion that an international drug monitoring system for the processing, storage, recovery and linkage of data on adverse drug reactions provided by national centres is a practicable undertaking, future development of the project can be envisaged.

44. The transmission and recording of reports from participating countries to the WHO Centre, which has been developed on a pilot scale, can be readily adapted to absorb the total output of each national centre. Computer techniques are now available to handle large amounts of data allowing early review of possible associations between drugs and reactions together with the dissemination of this information to national centres. Experience in the national centres has demonstrated the value of monitoring and has developed the basic techniques of evaluation.

A primary operational phase

45. The project could now move into a primary operational phase, the objectives of which would be as follows:

(a) Further develop and adjust the methodology evolved during the pilot phase for an operational international system of monitoring adverse reactions to drugs utilizing case reports submitted by national centres;

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[1] Off. Rec. Wld Hlth Org., 140, Annex 21, pages 91-92, para. 3.3.2, (Monitoring of Non-communicable Diseases and Conditions).

(b) undertake the recording and analyses of submitted data and their feed-back to national centres on an operational basis in order to determine suitability and usefulness of data presentation;

(c) provide facilities for searches by WHO and the national centres of stored data;

(d) study the mechanisms by which reports from additional drug monitoring centres can be included in the operation; and,

(e) study the contribution of an international drug monitoring system to national programmes for drug efficacy and safety, research in therapeutics and pharmacology.

46. The WHO Centre has already made considerable progress in the development of drug reference lists and of recording systems for drugs and adverse reactions. During the primary operational phase, these methodologies, together with additional computer programmes for routine analyses, alerting signals, and special file searches, can be expanded and adapted to meet the requirements of a fully operational phase.

47. It is anticipated that additional national drug monitoring centres may be in a position to contribute reports to the WHO Centre in the future. Increasing benefits are likely to accrue from the availability of information on the adverse effects of drugs from a wide range of countries.

48. Once the WHO Centre is in the primary operational phase, all countries, including those not participating directly, would be able to benefit. By augmenting drug safety evaluation in countries with national monitoring systems, more meaningful information on drug hazards could be provided by WHO to all its Member States. The speedier accumulation of evidence that warns all countries of a particular drug hazard, and the facilities for effective inter-change of information on a range of important and perpetually changing problems, should assist all countries to reduce their drug-induced illnesses and deaths.

49. Provision would be made for detailed studies of technical development, including the value to national centres of information disseminated during the primary operational phase. A comprehensive programme assessment should be undertaken, preferably no later than three years after entering the primary operational phase and provide recommendations for the development of a fully operational system capable of receiving, analysing and disseminating meaningful information on adverse reactions to drugs to member countries.

Management Assessment

50. During the forty-fifth session of the Executive Board[1] the Director-General expressed his intention to undertake a cost-effectiveness study of the project. The study was carried out with the purpose of establishing:

(i) a detailed work plan for the primary operational phase;

(ii) the necessary requirements for implementation of the primary operational phase, e.g. manpower, supplies, equipment, computer time;

(iii) the costing of these requirements, taking into consideration the alternative location of the project in Alexandria, Virginia, United States of America as at present or at WHO headquarters, Geneva.

[1] Off. Rec. Wld Hlth Org., 182, p. 54

51. The cost-effectiveness study included visits to:

(a) the WHO Drug Monitoring Centre, to perform a detailed evaluation of the pilot phase of the project, its system development, workload and staffing so as to determine the resources required to meet the needs of a primary operational phase;

(b) two National Centres, to gain information concerning monitoring systems in operation at the national level.

Close collaboration was maintained between the project and WHO headquarters technical and management staff to ensure that the data used in the study were sufficient and accurate.

52. The findings and conclusions of the cost-effectiveness study can be summarized as follows:

(a) Systems assessment. It was concluded that, from a management point of view, the system developed during the pilot phase for processing, recording and retrieving data relating to adverse reactions to drugs was sound.

(b) Work plan. The individual activities to be executed during a primary operational phase were determined, and an organizational plan developed to ensure optimum workflow.

(c) Manpower requirements. Based on a detailed workload study the following staff would be required:

> three medical officers, one scientist, one statistician, two programmer analysts, two technical officers, three technical assistants, one administrative assistant, two secretaries, one clerk, two key punch operators.[1]

In addition a medical officer and a key punch operator would be required as from 1 January 1972.

It is estimated that no additional staff other than those indicated above would be required to process input up to 5000 adverse reactions case reports per month. In the event the number of reports available either from existing or from newly created national centres to the WHO Centre would exceed 5000 per month, a reassessment of data handling methodology would have to be undertaken and staff requirements determined in the light of such an assessment.

(d) Location of the project. Two possible sites for the project were considered, i.e. Alexandria, Virginia, United States of America and WHO headquarters, Geneva.

If the project is located in Geneva, its cost would be less. Comparative costs in 1971 and 1972 for either location are shown in Fig. IV in the section on Budgetary Requirements and Financing. In addition, consideration should be given to non-quantifiable advantages of the location in Geneva, such as easier communication with the national centres and closer relationship with other technical sectors of WHO headquarters, as well as the availability of the programme support services at headquarters. Moreover, the computer system for the project has been developed to be compatible with headquarters' computer facility.

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[1] At present key punch services are provided under the grant from the Government of the United States of America.

Budgetary requirements and financing

1970

53. As reported to the Executive Board at its forty-fifth session, funds made available through a grant from the United States Government for this project lapse on 9 May 1970. The estimated obligations to continue the project to 31 December 1970 in its present location and under the existing arrangements amount to $ 156 500. In response to a request to the governments of the 10 countries participating in the project, voluntary contributions amounting to $ 52 322 have been made available to partly finance the continuation of this project beyond its expiry data. The United States Government has authorized the use of savings, accrued within the present allocation for the grant, beyond 9 May 1970 and estimated at $ 62 317. As a consequence, the shortfall to be found from other sources to finance the continuation of the project to the end of 1970 is reduced to an amount of $ 41 861. The Director-General hopes that voluntary contributions will be forthcoming to meet this deficit.

1971 and 1972

54. On the basis of the technical evaluation of this project and on the cost-effectiveness study completed in April 1970, budget estimates for a primary operational phase have been developed and are summarized in the following table. These take account of the changes in the staff requirements for 1972, whereby two new posts - one medical officer and one key punch operator - have been provided for as from 1 January 1972. Every effort has been made to keep the estimated requirements for 1971 and 1972 at the minimum level at which the project could operate effectively. The following table shows the estimated costs for both 1971 and 1972: (a) if the project remains in Alexandria (United States of America); and (b) if it is transferred to Geneva.

FIGURE IV

Purposes of expenditure	Estimated costs in Alexandria (USA)		Estimated costs in Geneva	
	1971 US $	1972 US $	1971 US $	1972 US $
Personnel	232 700	259 400	233 200	266 700
Duty travel	20 000	20 000	16 000	16 000
Consultants	26 000	26 000	12 600	12 600
Meetings			14 000	14 000
Communications	12 500	12 500	12 000	12 000
Production and distribution of documents	13 500	13 500	12 000	12 000
Rental and maintenance of premises			9 000	9 000
Rental and maintenance of equipment	75 000	80 000	4 000	4 000
Office supplies and services			14 400	14 400
Computer services			-	-
Cost of removal to Geneva			17 800*	
Total	379 700	411 400	345 000	360 700

* Non-recurring costs.

1971

55. Recognizing the importance of ensuring the continuation of this project, the Director-General has carefully reviewed his proposed programme and budget estimates for 1971 as contained in Official Records No. 179 with a view to identifying activities which might be postponed, the related funds being diverted to meet at least part of the costs of the project in 1971. The following three possible ways of financing the project in 1971 are presented by the Director-General to assist the Assembly in its consideration of the subject.

Possibility 1

56. Add the total estimated costs of either $ 379 700 (at Alexandria, United States of America) or $ 345 000 (if transferred to Geneva) to the Director-General's regular budget proposals for 1971 as contained in Official Records No. 179.

Possibility 2

57. In accordance with resolution WHA19.7[1] of the Nineteenth World Health Assembly, the Director-General's proposed budget estimates for 1971 include the last of five instalments of $ 100 000 to increase the level of the Revolving Fund for Teaching and Laboratory Equipment to a total of $ 500 000. The Director-General has included an amount of $ 168 848 in his 1971 budget proposals to provide for a phased implementation of the Health Assembly's decision to further extend in 1971 the use of the Russian and Spanish languages in the Health Assembly and the Executive Board.[2]

58. Should the Assembly decide that the implementation of one or both of these items could be postponed, the remainder of the estimated costs of the project could be added to the 1971 programme and budget estimates as contained in Official Records No. 179. Depending on the location of the project the amounts to be added to the 1971 budget proposals would be as follows:

Assumed postponement of	Alexandria (USA)	Geneva
	US $	US $
1. Revolving Fund for Teaching and Laboratory Equipment	279 700	245 000
2. Extended use of Spanish and Russian languages	210 852	176 152
3. Both items 1 and 2 above	110 852	77 152

Any postponements other than those suggested above or cuts would affect programme activities, and the Director-General would accordingly not recommend them.

Possibility 3

59. Should postponement of the implementation of one or both of the items referred to in Possibility 2 above be decided upon, voluntary contributions could be made by the Member States directly participating in the primary operational phase of the project to cover the balance required for operations in 1971.

1972

60. Whichever method the Assembly approves for financing the project in 1971, the Director-General requests that the Assembly consider the method of financing in 1972 and following years and its implications for future budget levels.

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[1] Handbook of Resolutions and Decisions, 10th ed., p. 349.

[2] Off. Rec. Wld Hlth Org., 176, 6 (resolution WHA22.11).