Harmonization of data fields for electronic transmission of case-report information internationally

Report of CIOMS Working Group 1A
on international reporting of adverse drug reactions

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Preface

The report which follows represents yet another product of an extremely productive and worthwhile process - further deliberations of the Working Group on drug safety of the Council for International Organizations of the Medical Sciences, (CIOMS). However, it also represents a departure from the usual processes by which these reports have been developed. Therefore a few introductory words seem necessary to put this report into perspective.

Like its companion reports (CIOMS I on international safety alert reporting; CIOMS II on international periodic safety reporting; and CIOMS III on international core safety information), this report has been generated by an unusual and unusually productive group of expert leaders in the field of drug safety. The CIOMS Working Groups have convened the chief safety officers from major regulatory and industry bodies to consider problems and challenges faced in the international conduct of activities necessary to assure the protection of the public's health relating to pharmaceuticals. Fundamental to the success of the effort is the willingness to recognize that all approaches can be improved; the desire to achieve the best for the people who take medicines independent of prior positions and practices; the willingness to roll up their sleeves and actually test such approaches before recommending them to others; and a desire for the broadest possible airing of their views as they evolve. While meeting to discuss scientific and technical approaches to the development of core safety information (CIOMS III), this group also addressed the ongoing activities to implement recommendations of the prior Working Groups. The rapid evolution of information technology, the desire to minimize duplicative reports, evolving regulation and rationalization in the European Union, proposed regulatory improvements in the United States and a desire to harmonize regulatory practices in Europe, America and Japan have all benefited from the earlier and contributed to the further deliberations of this group. Among emerging issues for the Group was the possibility of specifying, for automated record exchange, the data fields necessary for the various actors and agents in the process, a subject of which the Group had considerable experience and expertise.

But here the process by which this report has been developed deviated from all prior approaches. The Working Group undertook to "brainstorm" data field considerations as an add on to an existing effort. Thus, the activity, in contrast to other Working Group efforts, was undertaken without fanfare and broad external involvement or creation of a "separate" group. The Group worked quickly and informally, without field testing or having pilot projects. Thus, the work product as well represents a substantial deviation from the usual approach... this is very much a "Working Document." Finally, also unlike its other ongoing work, the Working Group does <u>not</u> plan to continue with this data fields project or related follow-up activities.

The Group debated and determined to issue this report in a format which clearly distinguishes it from other reports of the group, so that it may be clearly understood in this context.

Thus, the work is provided in a spirit of contributing to the debate and the ongoing work of others. It is the hope of the Working Group that those working on the very important and highly technical issues relating to automated information exchange will find its comments useful and allow them to speed society's way down this important path.

Zbigniew Bankowski
Hugh Tilson

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Introduction

This CIOMS activity has differed from previous efforts of the Working Group since it was accomplished alongside other work, notably CIOMS III–criteria for inclusion of information in the core safety data information. Not all the usual Working Group members were continuously involved, but the list below shows the principle involvements by Working Group members, though others have contributed to the discussions. Sue Roden and Minna Harengerd provided administrative support.

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Another aspect that is different with CIOMS 1a is that no pilot study has been performed. This has been because of the need to complete the proposals to fit in with the International Conference on Harmonization (ICH-3) work in this area. It also seemed to the Working Group that implementation of the proposals was dependent on regulatory acceptance and also needed informatics input. This will be best achieved by giving the proposals to the ICH, for their consideration. It was also decided to indicate the preliminary nature of these proposals by their publication in a loose binding, so that there will be no confusion over a more definitive publication by ICH.

Background

For 25 years the WHO Programme has had a set of data fields for transmission of ADR report information from national centres to the Collaborating Centre in Uppsala. These fields were based on the paper-based reporting forms, and, as such, are unnecessarily limiting for today's electronic transfer of information.

In 1989, after a series of CIOMS sponsored meetings, there resulted an agreement on a format for the international transmission of adverse event information by the pharmaceutical industry to regulators. This too was a paper based format -the so called CIOMS I form. This initiative was very successful and resulted in a mass of medically important international industry data which was not previously readily available to many regulatory agencies.

In 1991, at their annual meeting, a majority of WHO Collaborating Programme member states expressed the wish to be able to have access to the CIOMS I report data from a central source and in an electronic data format to increase efficiency in data management.

Also, as part of the ongoing deliberations of the continuing CIOMS Working Group on drug safety, convened as CIOMS III to focus on core safety information, the Working Group sustained its considerations of the impact and continuing need for further work of the prior two reports, CIOMS I on immediate reporting and CIOMS II on periodic safety reporting.

Consensus rapidly emerged regarding the international need for more efficient and rational exchange of safety information, particularly for more rationally structured approaches to the exchange of automated data in the face of rapidly evolving technology.

The Group agreed to institute a separate related project, to be conducted in parallel with the central focus of CIOMS III on core safety information, to propose a way forward for the creation of shared automated data globally. The effort was conducted under the code name CIOMS IA, based on an initial concept that the data contained on the CIOMS I form could be exchanged electronically among stake-holders.

Initially, deliberations were conducted by a small ad hoc subgroup of the CIOMS III Working Group with specific interest in electronic data exchange. However, as the project grew in scope, complexity and interest, it became "adopted" as a formal sub- project of the CIOMS III Working Group, eventually with all members participating in the development of final consensus and this report.

At its initial meeting (Chicago, June 1993), the Group agreed on the scope and general approach of the task. Reviewing current problems and barriers to effective and timely communication, the Group reviewed the proposals for the development of a centralized agreed set of data fields (the European Community CARE Project) (March 1993).

At its second meeting (Paris, 18 September 1993), the Group agreed on an outline of work and of general data fields to be described; technical assistance was sought to assure conformance of expectation with the realities of modern scientific computing. Following discussion at this meeting, proposals were put forward to the CIOMS III general Working Group for discussion and further refinement. At a third (and final) general meeting, Stockholm, Sweden (2 September 1994), the Working Group reviewed, in detail, the specifications for each automated field necessary for the creation of a centralized automated database. In addition, a series of data exchange principles and coding conventions were developed. As a result, this draft report has been assembled for wide distribution among stake-holders prior to developing the final recommendations of the task force.

It should be noted that the subject of standardized international data fields for ADR reporting will be a topic developed under the International Conference on Harmonization, ICH-3. This CIOMS 1A proposal will contribute to the ICH work to improve the transmission of regulatory information.

A Vision of a Paper-Free System

The Working Group envisions that all stake-holders, in assuring the safety of pharmaceutical products, will harmonize their practises and pool efforts regarding documentation and sharing of vital safety information. As introduced by the CIOMS Working Group I on safety alert reporting and CIOMS Working Group II on periodic safety update reporting, the notion of a single internationally agreed shared safety database represents a vital next step. It is believed that the principles and guidelines proposed by the CIOMS IA Working Group will assist in moving forward the debate and will hasten the time that such a single shared database becomes reality.

The current situation with safety reporting involves redundancy, multiple reporting, avoidable delays and the possibility of double counting and misinterpretation. For example, currently, safety data received by a regulator in one country might be entered into the national regulatory database, and shared or made available to the local manufacturer. This manufacturer might re-enter the data into a second database and transmit that data to other company affiliates in other countries where it might be entered into their database. Individual regulatory authorities under the CIOMS standard might

require that the information on a serious and unlabelled case, now known to a company affiliate in their country, be transmitted to them. That regulator might then also enter the case into a fourth database. Concurrently, the regulator in the first (or potentially in other, secondary countries) would probably have forwarded the case to the WHO Database. While prior customs and practices might have excluded one or another "stake-holder" from viewing one or another case at one or another stage in its "official" lifetime, more and more, national freedom of information laws and enlightened data sharing policies have led to methods of ensuring the privacy of patients and doctors while making the vital safety information available to those with a "need to know" because of a responsibility to act to protect the public health, including national regulators, the product licence holders and manufacturers, and multinational health bodies. To reduce these inefficiencies, delays and duplication of effort, the Working Group has considered the development of a single, global shared data set. The desired attributes of the data set include speed, quality, utility, economy, efficiency, consistency, and knowledge . In order to achieve this, the Group declared four working axioms:

* The Shared Work Principle: the roles of each of the major actors within a network of global safety data need to be agreed and fulfilled. Each manufacturer/licence holder must ensure follow-up and complete information on all of their direct adverse event/reaction reports and assure that these reports be accurately and rapidly submitted to the central repository; likewise, each regulatory authority must recognize the need for, and undertake, follow up and data communication.

* The "Single Intermediary" Principle: Information should undergo the minimum of processing steps between primary source and shared area.

* The "Essential Signalling Data Set" Principle (see 'shared area' below): There should be single global data set to which all important data describing the safety experience with a medicinal product are registered and into which those needing to generate a "signal" can gain continual access. It is envisioned that the data in this area will be spontaneously reported case data. Data collected in a structured way will also be included and identified.

* The "Multiple Stake-Holder" Principle: It is agreed that for international drug safety monitoring and public health protection, multiple regulators and multiple licence holders will need access in various ways to various portions of the shared data set. Data management should be centralized; data entry should be decentralized; the rules for accountable update and editing agreed; and "read- only" access systems generated.

All of these activities, fully compatible with the protection of individual privacy can and must be achieved in the near future to ensure that the tools now available to us are properly harnessed to advance and protect the public health.

Basic considerations

For drug safety professionals, perhaps the ideal situation is to have access to the complete information surrounding any case report worldwide. In the future, distributed data bases will allow such access; however, the seamless querying of multiple data bases is dependent either on identical data fields or upon software that will allow conversion. In addition to practical considerations, confidentiality issues (particularly concerning individual patient and doctor identification) as well as procedural issues (e.g. who is sanctioned to follow up case information), are likely to limit such open access. Also the need to have access to complete textual information is unnecessary for signal generation.

Consideration of the above issues led the group to the concept of a '**shared area**' for international signal generation. The shared area would contain as much information as possible on each case record commensurate with confidentiality and utility. Whilst it was thought desirable to include as much information as is available to complete the shared data fields, unavailability of any elements should not preclude the submission of the case report to the shared area.

It is clear that the shared area is conceptual rather than defined– it could be a single data base or multiple data bases and the mode of entry and access to the shared area has not been defined.

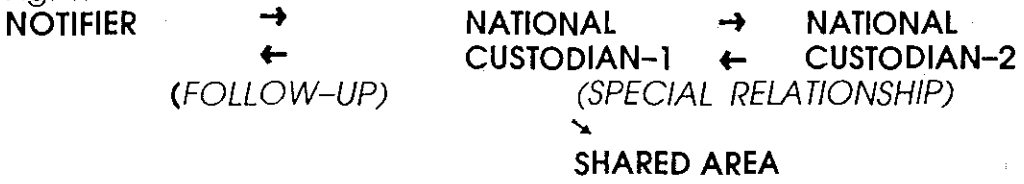
As work proceeded it was clear that there were some fields that might be regarded as alternatives or not absolutely essential in the shared area. These were designated as '**optional**'.

Some fields were considered necessary to satisfy some regulations, but not essential for the signal generating process. These fields have not been included in the shared area but are designated as '**available fields**' with the notion that at least these fields would be available for transfer by request under certain circumstances.

It should be re–emphasised that the data fields considered by the group were those necessary for signal generation. The needs of good pharmacovigilance practise within an agency have not been considered, nor, as stated above, the specific legal requirements which pertain to some countries.

For clarity, the primary reporting health professional was designated as '**Notifier**'. The primary recipient of information (either regulator or from industry) from a health professional was designated as '**Custodian–1**', thus implying primary responsibility for maintaining these data and their transmission. '**Custodian–2**' was the industry or regulatory agency in a given territory with a formal relationship to Custodian–1 in respect of sharing pharmacovigilance information. The relationship envisaged between the various parties and the shared area is given in Fig.1.

Fig. 1.



NOTES:

- National Custodian-1 could be manufacturer or regulator. NB. manufacturers may have their own internal arrangements for pooling and control of data internationally. This does not constitute a 'shared area' as used in his document, but relates to the internal arrangement of how manufacturers fulfill their 'custodian-1' obligations.

- Special Relationship between local regulators and local manufacturers.

- Shared area should be arranged by drug and available for review by:
  All regulators
  WHO
  Relevant manufacturers

- The case numbers serve to identify National Custodian-1.

Process

The procedure followed to determine the shared area was to amalgamate information from some industry and regulatory sources together with the WHO Programme data fields. The fields themselves were considered for the minimum number and type of characters that they could contain. For this purpose, internationally accepted abbreviations were considered desirable and have been adopted as far as possible. It is clear that there is some competition for recognition as the international standard, and it was beyond the scope of the Group's discussions to make value judgements in this area. Thus reasonable and workable abbreviations in use internationally are proposed but review and revision in the light of comment must be considered.

Following early discussions, draft versions of the fields have been circulated amongst the CIOMS Working Group and their technical advisors for comment and discussion, but unlike the situation with some previous CIOMS work in drug safety, the proposals are put out for consideration before a pilot study has been undertaken.

Proposed Data Fields and explanation

Note: S.A. = Agreed Shared Area
A.F. = Available fields
O. = Optional

A # indicates the space for a character, with text associated indicating how the space should be completed. Sometimes the text is very specific giving abbreviations to be used in **bold** text. # – 22 indicates a 22 character string is the maximum allowed in that area, and is based on accumulated experience within the Group. Where the Group could not reach a definite decision based on experience, # – ? has been used.

Dates follow the convention:	# #	# # #	# # # #
	day	**month**	**year**
	numeric	alpha	numeric
e.g.	09	sep	1993

Partial dates will be completed with '0' for missing data:

e.g.	00	000	1993

1. Case report identification

S.A. **1.1 reference numbers (incl. country and origin of report)**

It is essential that the Case Report Identification brings together sufficient pieces of information in order to uniquely identify each transmitted report. The first section of this "identifier" refers to the origin of the transmission, i.e. manufacturer or regulator. The second section applies to an unique number to identify the transmitter. This number must be allocated and controlled by an agreed central authority, such as the WHO. The third section refers to the country of the transmitter and the country code used should be in accordance with an internationally agreed standard. Finally the fourth section refers to the case reference number. It was considered that this number should be the first number allocated locally and should never be changed. If for some reason the number were to be deleted then the deleted number should never be re– allocated.

Use:
for **M**anufacturer/**R**egulator to whom report was first sent (custodian-1)
for pre– allocated identification number for manufacturer
for country of regulator/ manufacturer (WHO and ISO, 3 character)
###,###,###,###,### for case number determined by custodian–1

S.A. **1.2 country where reaction occurred**

Use:
(again WHO and ISO 3)

S.A. **1.3 organisation entering case into shared area**

Use:
###
i.d. country

(If different from Custodian–1: should be automatic from 1.1. e.g. In most cases it will be Custodian–1 who enters the case in the international shared area; however, the case may come from, say, a country where an international company is represented by another organisation which reports to a regional office of the international company in an adjacent country. Then the other organisation will be Custodian–1, but the international company may be the party entering the case into the shared area).

A.F. **1.4 country where drug was obtained**

Use:
###

A.F. **1.5 country of notifier**

See Section 5.

Use:
###

S.A. **1.6 dates**

Use:

##	###	####	for date Custodian–1 first became aware of report
day	month (alpha)	year	
##	###	####	for date last follow up information received by Custodian–1
##	###	####	for date received by Custodian–2
##	###	####	for date received by WHO

Need 4 digits to cope with change in millennium, but could be pre–programmed.

S.A. **1.7 special features of report**

It was considered that it would be helpful to the recipient to include in the administrative section the reason for the transmission of the report. The reasons listed would be related to the guidelines which define national and international reporting requirements. Completion of this field is applicable therefore to the National Custodian-1 and not the notifier (primary reporter). Reasons would be; adverse reaction due to drug interaction, drug abuse, drug misuse, unexpected lack of effect.

Use ## for :

Over**D**ose
Drug **W**ithdrawal (the event occurs after drug discontinued)
Drug **D**ependency/abuse
Drug **M**isuse i.e. outside labelling/non-therapeutic
Unexpected **L**ack of intended Effect (excl. clinical trial)
Note: with significant medical consequences (Examples)
Inter**A**ctions
Other

S.A. **1.8 type of report**

The group concluded that it is particularly important that the type of report being transmitted is clearly identified in order that the recipient can compartmentalise reports. This facilitates the identification and analysis of reports generated from the same reporting methodology. Examples of type of report would be spontaneous, post marketing surveillance (PMS) or special monitoring (Prescription Event Monitoring – PEM), clinical trial. Also it was recognized that where a report originates from a publication then it is important that this information is recorded and transmitted. It was agreed that space should be allocated to allow the citation to be associated with the "type of report", i.e. spontaneous report: published, then journal citation.

Use # for:
s – **S**pontaneous report (direct)
Use # for:
p – **P**ms/special monitoring e.g. Prescription event monitoring published)
Use # for:
t – Clinical **T**rial
Use # for:
e – **E**xpedited

And then use # for :
Y or **N**, if published **Y**es or **N**o

For literature reports, record reference using Vancouver conventions agreed for citations. Space for citation needs to be allocated.

2. Patient characteristics

Fundamental to the international shared data set principle is the individual patient 'building block' logic. Each case in the data base reflects the experience of an individual patient... one of the three fundamental requirements for the safety signalling system (a person, a drug and an identifiable adverse event). The governing principle of internationally shared patient characteristic data is that information adequate to understand the specific characteristics and attributes which might contribute to the adverse experience must be available while sheltering the individual from possible privacy concerns.

A.F. **2.1 patient identification**

This information is generally maintained by the notifier. However, a patient identifying code between the notifier and the first national custodian is also necessary so that further mutual communication is possible – from the reporter to update with new information and from the custodian for further clarification requests as needed.

However, under no circumstances should such patient identifying codes be shared further.

A.F. **2.2 patient origin (e.g., city of residence)**

This is likewise necessary for further case follow up. However, it should not be shared centrally.

S.A. **2.3 age at time of reaction**

Age is an important potentially explanatory variable for drug safety. The data convention is as follows:

(a) Use *###* for:
a numerical field, right justified

(b) Use # for:
Days or **M**onths or **Y**ears

S.A. **2.4 date of birth**

A date of birth is also needed. Because of the possibility of adverse drug experiences in the elderly, a provision is necessary to ensure the registration of centenarians. To that end, four blocks are required for the year of birth.
Use:
####

S.A. **2.5 gender**

The gender is likewise an important explanatory variable: Four options are provided. The creation of a special category for persons undergoing sexual transition is deemed particularly necessary and appropriate for the monitoring of pharmaceutical, biological and devices safety issues because of the frequent use of these agents during such transitions.

Use # for:

- f – **F**emale
- m – **M**ale
- u – **U**nknown
- o – **O**ther (sex transplants etc.)

S.A. **2.6 background data**

Extensive background data will doubtless be collected by the national custodian and/or be available from the notifier. These would include information on relevant medical history; relevant family history; previous drug reactions; predisposing factors; concomitant illnesses; occupational problems... and perhaps many others. The Working Group considered delineating separate data fields for each of these. However, internationally agreed coding conventions are not available; many of them represent complex and often extensive individual data sets (e.g., relevant medical history). Most importantly, extensive background data are useful for detailed case analysis in the event of a signal. However, for the purposes of generating a signal, they need not be held centrally. Thus, for the central (shared) area, the Working Group recommends a single binary code to reflect the availability of background data held by the national custodian:

S.A.

Use **(Y)**es or **(N)**o, for availability of background information in Custodian-1 data base:

- # medical/clinical history
- # family history
- # previous drug reactions
- # predisposing factors
- # concomitant illness
- # occupational history

However, two special provisions are made:

(1) For concurrent illnesses requiring concomitant medications, each medication should be encoded (see section 4) and each major indication for these concomitant medications reflected by a linked ICD 10 code (see section 4.15 below). Thus, concurrent illnesses are available elsewhere in the database.

(2) The Working Group recognized that to expedite analysis of potential signals and to reduce the need for multiple inquiries for further detail from the national custodian, a very limited free text field (approximately 500 spaces) should be made available.

The Working Group adopted the following principles regarding 'free text' discipline:

* Information should only be entered if not available in a pre-coded field elsewhere in the data set.

* Only information which provides additional facts (not opinions) should be provided.

* Priorities should be given to facts likely to permit proper interpretation of the reaction. This is in keeping with the spirit of the "free text" block on the CIOMS I form (# -21, i.e.. a field containing up to 21 characters).

2.7 special reporting

2.7.1 parent-child reactions

Parent-child exposures: Special reporting and patient tracking challenges present themselves under circumstances in which a parent may have been exposed to a drug and indirectly (e.g., via placenta or breast milk) have exposed a fetus or infant. A reaction may have occurred in the child only (in which the child is the only case), or in both the parent and the child (in which two separate but linked cases should be created), or in the parent only but the child's (or fetal)exposure and positive outcome are of interest. Under these circumstances, it is important to have data fields that are identifiable as related to the parent (in the case of an infant report), to the child (in the case of a parent report) and linking the two cases (in the cases of two separate adverse reactions) by cross- reference to case reference numbers.
More rarely these reports may relate to multiple births. In such cases a report and report number need to be generated for each child suffering a reaction(s) and again the reports need to be linked via cross reference.

Additional fields needed in patient section are as follows:

-the usual **Parent Details** with additional information on gestation time in respect of the mother,

-the **Child/Fetus Details** should include if available the sex, weight in kilograms, gestation period at birth or evacuation, and the related parent report number if the parent also suffered a reaction,

–the **Drug/Product Information** differs from the usual report in respect of the route of administration. The normal routes of administration apply to the parent but for the child the following routes could apply;transplacental, transmammary, uncertain (although it is known that the parent took the drug(s), subsequent exposure of the child/fetus to the drug(s) is uncertain), not applicable (this applies when it is known that the parent took the drug(s) and that the child/fetus was not exposed to the drug(s)), direct (this reflects the fact that the drug(s) was given directly to the child/fetus), paternal (this applies when the child/fetus was exposed to the drug(s) as a result of the father taking the drug(s)),

–all other drug/product information relates to the parent, i.e. dose, start and stop dates. Gestation period at the time the mother took the drug(s) is also included.

S.A. (i) **In infant report**

Fields for parent(s) details as for any case report (see 2.1– 2.6).

Plus, for an exposed father:
estimated date of conception: *## ### ####*
events/illness in father?: # **Y**es or **N**o

If 'Yes', father's case record number:
 # ###### ### ###,###,###,###,### (see section 1.1)

Plus, for an exposed mother:
estimated date of conception: *## ### ####*
(point in gestation of exposure can be calculated from drug start date)
events/illness in mother?: # **Y**es or **N**o

If 'Yes', mother's case record number:
 # ###### ### ###,###,###,###,###,### (see section 1.1)

S.A. (ii) **In parent report**

Fields for child / fetus details as in any case report (see 2.1–2.6):

– *##* (weeks) for gestation period when drug(s) taken (maternal report only).
– *###* (kg) weight at time of reaction or birth weight
– *##* (weeks) gestation period at birth / evacuation
– events/illness in child?: # **Y**es or **N**o

If 'Yes', child's case record number:
 # ###### ### ###,###,###,###,###,###

Special Conventions:

* Premature termination of pregnancy: Code the mother only. If the child has only compilations of prematurity (i.e., no birth defect or drug–related disease) no additional cases created.

* Spontaneous abortion: Code only to mother.

* Spontaneous abortion with abnormal products of conception diagnosed by laboratory examination: Create two cases. The abnormal conceptus is coded as for infants (above). The pregnancy loss is coded for the mother.

* Therapeutic abortion for defect: Code only to infant.

Drug exposure information is coded as for all cases (see section 4), the normal route field holds for the route to the parent. In addition, however, mandatory fields must be coded for the child. For this reason added to the usual exposure lists are:

S.A.
##– **trans**placental
##– **trans**mammary
##– **mat**ernal (parent took drug, exposure of child uncertain)
##– **n**ot **a**pplicable (parent took drug but child not exposed)
##– **direct** (drug direct to child)
##– **pat**ernal

In the case of a drug directly administered to the child/infant, indication of route of exposure would be as in 4.10.

Other Drug Information: Dose start and stop dates and individual and concomitant medications relate to the parent for intra–uterine exposures.

The free–text field for history may be required for information regarding the mother in the event of a single infant case report or the infant in the case of a single mother case report (see 2.6)..

2.7.2 reaction to drug used in treating an existing reaction

Although this is rare, it may occur. Each incident should be judged as separate i.e.. a separate report for each drug, but linked with cross reference to record numbers (see section 1.1)

3. Event or suspected reaction

This section should be open ended and allow for all events notified, that is, the following fields should apply to each separate event, whether it is a symptom, sign, diagnosis or other description of a distinct event.
The terms used should reflect notifier's terms as closely as possible in recording a diagnosis when reported.

3.1 suspected reaction/event dates

S.A. Use ## ### #### for:
both date of onset and resolution of suspected reaction/event.

For symptom complexes, the date of the start of the complex set of symptoms should be recorded in the shared area. It is expected that Custodian-1 will keep a narrative chronology of the symptoms and signs, as originally reported by the notifier.

If either or both dates are not available, use ## for duration as a number, and use ## for duration unit from the table:

Code for duration	Duration time unit
SE	Second
MI	Minute
HR	Hour
DY	Day
WK	Week
MO	Month
YE	Year

No case sensitivity: both lower or upper case can be used

And use # for :
C: Duration counting forward to time event commenced
S: Duration counting back from time event stopped/patient seen by notifier. The reason for this 'C' and 'S' notation is to be able to fix any given duration to a firm date. If this method is used it is possible to perform other calculations on data, if necessary, which would be impossible otherwise.
The Working Group generally held the view that fields should not contain Custodian calculated data: only actual data or estimates reported by the notifier should be entered.

Examples:
If a report only states that the patient was seen on the 25th March 1990, with a one month history of vomiting, the appropriate entry would be:
25 mar 1990 1 mo s
Or if the patient had a month of vomiting starting on the 25th March 1990, the entry would be:
25 mar 1990 1 mo c

In both cases it would be possible to calculate the time to onset of symptoms from the drug administration dates.

3.2 events/suspected reaction(s) terms

Use #–? for:
S.A. verbatim in original language either/or
Use #–? for:
English translation
S.A. Use #–33? for:
preferred terms
Use # for:
an asterisk to denote most important events/reactions

S.A. **3.3 seriousness**

Serious – use # for:
Y= **Y**es
N= **N**o
Mark separately for each event

Use ## for:
Death
Hospital admission/prolongation
Life threatening
Disability
Congenital anomaly
Intervention (if medical action was taken to prevent a reaction from becoming serious. See below)
Other

Serious adverse events or suspected reactions have been defined by ICH-2, from which the following is paraphrased for guidance:

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is used. This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore special medical or administrative criteria are needed to define reactions that, either due to their nature ('serious') or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the intensity (severity) of a special event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

* *results in death,*
* *is life-threatening,*
  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
* *requires inpatient hospitalization or prolongation of existing hospitalization,*
* *results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.*

Medical and scientific judgement should be exercising in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

S.A. **3.4 labelled (i.e.. in product data sheet) or not**

The CIOMS Working Group II, in the International Reporting of Periodic Drug- Safety Update Summaries (CIOMS, 1992) , suggested that the manufacturer's core safety data sheet (international prescribing information) should be used as the basis for whether new events are included in the Updates or not. This decision was based on the logic that the core safety data sheet information would be a conservative document and that this would mean that new events might be overemphasized in their importance. This was a better bias than the reverse.
The group felt that a similar logic should apply to indicating whether or not an event is labelled for the shared area. It is, however, possible that regulators may use their Summaries of Product Characteristics or similar data sheets as the baseline when filling in this section, and some caution is urged in the interpretation of this field,

Use # for:
Yes or **N**o

and use # for reference standard:
Core safety data sheet (manufacturer's)
Local (national) data sheet
Other

S.A. **3.5 patient outcome**

Use # for
A – abated/recovered without sequelae
B – abated/recovered with sequelae
F – not yet recovered/still present at time of report
D – death
U – outcome unknown

If "D" or "B" , use ## for:
Probable
Possible
No relationship
Unknown

to indicate if death or sequelae were attributed by the notifier to one or more of the adverse reactions.

S.A. **3.6 outcome of each event**

Use # for:
A – abated/recovered without sequelae
B – abated/recovered with sequelae
F – not yet recovered/still present at time of report
D – death
U – outcome unknown

The reason for separating the patient and event outcomes in 3.5 and 3.6 is to clearly show that a serious outcome for the patient might be unrelated to any or all of the reactions.

S.A. **3.7 death information**

Use ##### for:
reported cause of death (ICD 10)

Was a post mortem performed?
Use # for:
Yes or **N**o

And use ##### for:
post mortem determined cause of death (ICD 10)

Use ## ### #### for:
date of death.

S.A. **3.8 description of reaction in free text**

See also comment section in 2. It is proposed that there will be a single comment section of 500# , including all aspects of the case. It should be brief and relevant.

Amongst the information one might wish to include are the following:

-is the medical diagnosis well substantiated
-is hospital discharge summary available
-are there any inconsistencies in the information for this and other sections, particularly for dates
-have other non-drug causes been eliminated adequately
- is histology available
-are detailed laboratory test results available

Another set of fields indicating the availability of this information with Custodian-1,is a possible alternative.

4. Drug information

These fields apply to all drugs known to be taken by the patient in a relevant time period before the reaction.

S.A. **4.1 drug name**

Use #–39 for:
Trade name of product (brand name)

Use #
as an additional character to indicate the subject drug(s) which formed the basis for the notifier's report to Custodian–1.

S.A. **4.2 composition**

Use #–39 for each:
Generic name(s) or international non–proprietary names(s), if possible, of active ingredients only.

S.A. **4.3 dosage form**

Use # for :
Tablet
Capsule
Gel
Solution
Suspension
Sustained **R**elease Formulation
Aerosol

The above list is not exhaustive; many sub–categories could be added and will need consideration.

S.A. **4.4 WHO Drug reference list code (WHO Drug Dictionary)**

Use ########## (11 char) for:
alphanumeric code, but this could be either an automated field from the generic name(s) or selected from a linked WHO–DD

In turn the WHO drug reference list code contains links to:

- CAS (Chemical Abstract Service)

- ATC code (Anatomical Therapeutical Chemical)

The ATC code is a 7 character multi-axial alphanumeric code.
It refers to the:

- anatomical site (which part of the body is the target of the therapy)

- therapeutical (which therapeutic concept is represented by the drug)

- chemical class (to which chemical class belongs the drug)

Note that a given WHO DD code can refer to one or several ATC codes. Give the primary ATC code for the drug and given indication. This is especially important if no WHO DD code is available.

The CAS code is a 10 character numeric code that refers to a table of chemical substances. Note that for combination drugs there are several CAS codes. Give the primary CAS code for the drug. This is especially important if no WHO DD code is available.

The World Health Organization has details of all of the above, which could be included, as look up tables, in the software.

O. **4.5 CAS (Chemical Abstract Service) number/code**

Use ########## (10 char) for:
numeric code including leading zeros

This need not be used if the WHO drug reference number is used, since it can be automatically retrieved.

O. **4.6 ATC code**

Use ####### (7 char) for:
alphanumeric code

This need not be used if the WHO drug reference number is used, since it can automatically be retrieved.

Dosage schedule and route

- Dose and frequency at the time of the event

S.A. **4.7 Frequency of dosing**

The frequency indicates how many times per dosage interval unit the drug was given at the time of the event. Here only digits (or blank) are allowed. If you have only total daily dose, leave this field blank and enter the total dose under 4.8. Note that terms such as 'twice daily' or 'b.d.' must be noted as '2 dy'.

Use # for:
number per dosage interval as relevant
(if the dosage interval is given as 'long term' or 'as required (prn.)' do not use)

Use ## for:
dosage interval unit

Code for dosage interval	Dosage interval time unit
ON	Only once (single dose)
SE	Second
MI	Minute
HR	Hour
DY	Day
WK	Week
MO	Month
YE	Year
LT	Long term (>>1 year and continuing, for other drugs primarily)
PN	PRN (as required)
EP	Episodic

No case sensitivity: both lower or upper case letters can be used

S.A. **4.8 quantity (amount per dose)**

The quantity indicates the amount of drug given per intake at the time the event occurred. Give a number, if necessary, with a decimal point in position 2, 3, 4. The conventions in 4.7 are necessary to calculate the daily amount (together with 4.8).

Use ##### for amount (right adjusted number, with decimal point usable in # 2,3 or 4), & ## for unit code (see below)

Unit code list:

Code for unit	Unit list
BQ	Becquerel
DF	Dosage form (if other unit cannot be given, e.g. several ingredients or if exact dosage strength of a formulation is unknown)
DR	Dram
GM	Gram
GR	Grain
GY	Gray
IU	International units
KG	Kilogram
KU	International units (1,000)
LB	Pound
LT	Litres
MB	Megabecquerel
MC	Millicuries (milli=10–3)
ME	Milliequivalents (MEq)
MG	Milligram
ML	Millilitres
MM	Millimole
MO	Mol
MU	International units (1,000,000)
NG	Nanogram (nano=10^{-9})
NU	National Institute of Health Unit (Interleukin)
OZ	Ounce
PC	% (topical only)
PG	Picogram (pico=10^{-12})
UC	Microcuries (micro=10^{-6})
UG	Microgram
UM	Micromol

No case sensitivity: both lower or upper case letters can be used

S.A. **4.9 total quantity amount**

Total cumulative dose; where relevant, mainly intended for clinical trials. Same conventions as 4.8.

S.A. **4.10 route of administration**

Use ## for values from the Route of administration list below:

Code for Route	Route of administration
AU	Intra-auricular
BU	Buccal
CN	Intra-coronary
CO	Conjunctival
DE	Dental
EP	Epidural
IA	Intra-arterial
IB	Intravesicular
IC	Intracardiac
ID	Intradermal
IH	Inhalation
IL	Intrapleural
IM	Intramuscular
IN	Intranasal
IO	Intra-ocular
IF	Intraperitoneal
IR	Intra-articular
IS	Insufflation
IT	Intrathecal
IU	Intra-uterine
IV	Intravenous including perfusion
MP	Implant
PA	Peri-articular
PC	Percutaneous
PO	Oral
PR	Rectal

Code for Route	Route of administration
PV	Paravertebral
SC	Subcutaneous
SL	Sublingual
SY	Systemic
TM	Transmammary transfer
TO	Topical
TP	Transplacental
TR	Intratracheal
UN	Unknown/other
UR	Urethral
VA	Vaginal
VT	Intraventricular, cerebral

No case sensitivity: both lower or upper case can be used

4.11– 4.14 Dates for all drugs

S.A. **4.11 drug stopped**

Use # for:
Y if drug was stopped after event onset
N if drug was continued despite event
U if unknown if drug was stopped or continued

S.A. **4.12 drug start date**

Use *## ### ####* for date

Give date drug therapy started at whatever dose (use partial dates – month and/or year with zeros in other fields – if no full date is available, but some details are known).

S.A. **4.13 drug stop date**

Use: *## ### ####* for date

Give date drug therapy stopped at whatever dose (use partial dates – month and/or year with zeros in the other fields – , if no full date is available, but some details are known).

S.A. **4.14 Duration**

Use ## for duration as a number (if both dates are not known). Not relevant when only a single dose (ON) is used (below)

And use ## for duration unit from the table:

Code for duration	Duration time unit
ON	Once (single treatment)
SE	Second
MI	Minute
HR	Hour
DY	Day
WK	Week
MO	Month
YE	Year

And use # for :
C: Duration, counting forward from time drug was commenced
S: Duration, counting backwards from time drug was stopped

This variable indicates if the duration refers to the first or the last intake of the drug and allows for other calculations to be made.

S.A. **4.15 indication for use**

In this international shared area, use the ICD 10 code for each drug.

ie. use ###### for alphanumeric code

In the Custodian-1 data base it is likely that more data may be available, as free text fields.

S.A. **4.16 effect of dechallenge**

Per diagnosis or event suspected drug, use ##, right justified, for:
-y = yes
-n = no
-u = unknown
-na = not applicable

Dechallenge can be defined as significant reduction of exposure to the drug. It can be complete (withdrawal) or a significant reduction of the dose.

Effects are measured as a significant change in the symptomatology towards improvement.

The code **y** = yes should be used if such a dechallenge occured and an effect was observed, the code **n** = no if no such observation could be made after dechallenge.

The code 'unknown' should be used if it is not known that such a dechallenge actually occurred.

The code **na** = not applicable applies to the following situations:

-it is known that if dechallenge actually occurred, the dose reduction is not expected to manifest itself within reasonable time in decreased drug levels in the blood, in relevant tissues or at receptors ("long kinetics")

-the effect cannot be measured because it is dominated by concomitant treatment

S.A. **4.17 effect of rechallenge / re-exposure**

Per diagnosis or event, per suspect drug ## , right justified, for:

y = Yes
n = No
u = Unknown
na = not applicable

A rechallenge / re-exposure is defined as a re-exposure to the same drug product or active substance or a significant increase to the dosage after a dechallenge (see above) be it intentional (for diagnostic purposes) or accidental.

The code **y** = yes should be used if the same symptomatology recurs (take care in describing it in the event section).

The code **n** = no should be used if a rechallenge did not result in such re-occurrence.

The code **u** = unknown should be used if it is not known if a rechallenge actually occurred.

The code **na** = not applicable should be used if there was no rechallenge or its result could not be measured (see above).

5. Information concerning notifier

This section identifies the person who originates the report. The notifier may be a patient, health professional, or other person such as a lawyer.

The key features of this section are the **Country** and **Speciality** or **Status** of the possible duplicate reporting. Knowledge about the "speciality" status of the notifier provides information on the medical validity of the report. The **notifier**. Knowledge of the **notifier** country assists with the identification of terms allowed include; report from physician, other health professional, patient/relative, other e.g. lawyer. It was felt important also to be able to identify whether or not there was **Medical Confirmation** for a report originating from a source other than a medical practitioner.

It was agreed that confidential details pertaining to the notifier should be retained by the National Custodian–1 and not transmitted to the shared area. It was recognized, however, that there may be a requirement to provide this information to the local regulatory authority.

S.A. **5.1 country**

See 1.3a

S.A. **5.2 notifier**

Use ## for:

report from **Ph**ysician
ie. medically qualified person, licenced to practice or registered physician (ie. MD., DO., MB. ChB., LRCP. etc)

report from **Pharm**acist
ie. person licenced to practice pharmacy (ie. B.Pharm., BSc (Pharm)., MPS, etc.)

report from other **H**ealth **P**rofessional
ie. person qualified in a health professional area such as a nurse, dentist, midwife, nurse practitioner, optometrist, veterinarian, chiropractor, physiotherapist, etc.

report from **P**atient/**R**elative
ie. the person having the reaction/event or a person in a close relationship to the patient.

report from **O**ther (e.g. lawyer)
ie. any other person such as a lawyer, advocate, counsellor etc.

For clinical trial reports, record company's protocol number, using # –20? This is not for the shared area.

The primary custodian should retain all information necessary to contact the notifier (ie. name, address, telephone number). This information will not be in the shared area.

S.A. **5.3 medical confirmation**

Use # for **Y**es or **N**o

This information will be used to determine whether information provided by anyone other than a physician has been subsquently confirmed by a physician familiar with the case. If the notifier is a physician, this field should be coded 'Yes'.

6. Case report history

It was strongly believed by the group that any case report entered into the shared area should not be changed in any way which was not totally transparent. This section will therefore contain a complete audit trail and the data contained in the previous fields will be the most recent data.

S.A. **6.1 audit trail**

The paragraph numbers and headings used in the basic data fields should appear in this section if they have been modified in any way. They should be suffixed with 'old' (e.g. 'old 3.6 outcome of each event' would mean additional information has been entered with reference to para. 3.6) , together with the date (## ### ####), time (24h. clock– ####),and agent's identifier (##### ###) who was responsible for the change. In order to allow for updating of information,
–200 may be used for additional commentary.

S.A. **6.2 custodian–1 re–evaluation**

This section is to be used for a significant re–evaluation of the report. It was thought that the main reconsideration would focus on the events reported and the seriousness of the report. Therefore, use:

#–39, for each notified term (by the primary notifier)	#–39, for equivalent term(s) suggested by Custodian–1

This was seen as particularly useful when notified terms can be synthesized into a syndrome, for example:

Notifier's terms	**Custodian–1 interpretation**
Neutropaenia	) NEUTROPAENIA
Rash	)
Loss of consciousness	)
Hypotension	) ANAPHYLACTIC SHOCK
Sweating	)
Nausea	)
Pallor	)

Custodian–1's view of the seriousness and also whether the events are re–defined could also be documented here using the same conventions as in sections 3.3 and 3.4.

Thus, when there are no discrepancies between the notifier and custodian, the custodian's terms reproduce the notifier's. When there are discrepancies:

* the terms used by the notifier are listed and can be evaluated by all parties with access to the shared area.

* the custodian fulfills her/his medical responsibility by giving his/her interpretation of the nature and significance of the event.

S.A. **6.3 retrieval of information**

From Fig 1. it is clear that national Custodian-1 has the prime responsibility for obtaining complete information from the notifier. It is also clear that the custodians within a country have special needs for retrieving information from each other.

Suggestions have been made about some additional information fields ('available fields') that national custodians may wish to have available during the follow up of a signal based on the international shared area . These suggestions are not exhaustive in relationship to the situation within a national regulatory centre or a manufacturers organisation, since it was not the purpose of this group to influence the operation of any internal pharmacovigilance system.

Confidentiality must be maintained to the highest standards, therefore, for data retrieval, it will be wise to have the same procedure as for the audit trail, to know who accesses what and when. Thus each access to a report will be logged in this section, as follows:

the date (## ### ####),
time (24h. clock- ####),
and responsible agent's identifier (##### ###).

Chapter 2.
Some general ideas from the Working Group meetings

1. All spontaneous & serious suspected events (trials and PMS)

It was thought that all spontaneous events that occurred after a drug was first marketed in any country, as well as those from clinical trials and post marketing surveillance, that are serious and suspected to be related to the drug concerned, should be reported to the shared area.

2. Check lists for national Custodian-1

There should be check lists to indicate:

- A) What extra source data are available from Custodian-1, (e.g., histology slides, autopsy report, detailed laboratory data, hospital discharge summary, etc.)

- B) Availability of further background data, (e.g., previous drug reactions, concomitant drugs)

(NOTE: The purpose of the check list is so that should a signal be identified and on request, the further information would be made available.)

A "nice to have" suggestion was to indicate whether reported events were 'labelled' so that the reader would immediately be aware of what is/is not recognized (labelled) against core data sheets.

3. Key information and ideas useful in looking for signals.

The Working Group identified the following as particularly important in looking for signals:

- special features of report (e.g., dependency, interaction- see 1.7)

- "Seriousness" at event, as well as case level

- Greater focus on reason for death and whether related to event

- Distinction between things such as cyclical and PRN usage of drugs are necessary

- De-challenge and re-challenge results

- Composition of combination products

- Dates of all concomitant treatments

- Proposals for distinguishing parent from child (e.g., lactation effects)
- The short narrative for expanding some areas of the report
- Definitions and data field specifications proposed for:

  Serious
  Outcome
  Dose
  Route of administration
  Drugs (WHO DD)

Chapter 3.
Some important questions recognized, but not resolved, by the Working Group

The following issues were considered but left unresolved largely because they were not thought to be within the Working Group's remit

- Medical and adverse event/reaction terminology
- Ownership of data
- Responsibilities for management of any area including the 'shared area'
- Hardware/Software
- Need for good pharmacovigilance practices
- Duplicates, their recognition and reconciliation
- Eligibility for access to data

Chapter 4.
Preliminary issues raised by a separate working group during the annual meeting of national centres within the WHO Collaborating Programme on Drug Monitoring, Berlin, September, 1994

Whilst the working group had too little time to consider the detail of an early draft of this report, they were able to offer the following comments:

- Overall support for the work

- They would like to maintain their own national case identity number, which they preferred to be consecutive so that it was easy to see if the report was old or new

- If birth date is used then the onset date of the event is necessary to be certain of the patient's age at the time of the event, particularly if the report is delayed. However, birth date may reduce patient privacy to some extent. A major advantage of birth date was in identifying duplicates

- There was concern over the work involved in translating the free text fields e.g. section 3.8 to English

- They would like to see date of death and date of recovery added to sections 3.5 and 3.6. They also considered that 'permanent damage' should be added to reinforce 3.5A and 3.6A

Chapter 5.

Appendix 1.
A suggestion for the structure of the data base in an easy reference format.

Appendix 2.
A sample CIOMS 1 report

Appendix 3.
The CIOMS 1 report from Appendix 2. transformed into the suggested electronic shared area format

Appendix 1.

Suggested Structure of Database

Field Number	Variable Name or Description	Data Type	Field Length (Number characters)	Field Type*
1.1	Reference identification number	Alpha-numeric	19	SA
1.2	Country where reaction occurred	Alpha	3	SA
1.3	Organisation entering case	Alpha-numeric	9	SA
1.4	Country where drug obtained	Alpha	3	AF
1.5	Country of notifier	Alpha	3	AF
1.6a	Date of first notification	Date	9	SA
1.6b	Date follow-up information received	Date	9	SA
1.6c	Date received by regulator	Date	9	SA
1.6d	Date received by WHO	Date	9	SA
1.7	Special features of report (overdose, etc.)	Alpha	2	SA
1.8	Type of report (spontaneous, etc.)	Alpha	1	SA
2.1	Patient identification			Not shared
2.2	Patient origin			Not shared
2.3a	Patient age	Numeric	3	SA
2.3b	Units of patient age (days/months/years)	Alpha	1	SA
2.4	Patient date of birth	Date	9	SA
2.5	Gender	Alpha	1	SA
2.6	Background data available	Alpha	6	SA
2.7.1	Special reporting (parent-child reactions)			
2.7.2	Special reporting (reaction to treatment drug			
3.1a	Date of reaction	Date	9	SA
3.1b	Duration of reaction	Alpha-numeric	5	SA
3.2	Event term(s)	Alpha	39	SA
3.3	Serious/Death/Hospital, etc.	Alpha	2	SA
3.4	Labelled in product data sheet?	Alpha	1	SA
3.5	Outcome for patient	Alpha	2	SA
3.6	Outcome of event	Alpha	1	SA
3.7a	Death information	Alpha	11	SA
3.8	Free text info on event	Free text	500	SA

Field Number	Variable Name or Description	Data Type	Field Length (Number characters)	Field Type*
4.1	Brand name of drug	Alpha	39	SA
4.2	Generic name	Alpha	39	SA
4.3	Dosage form	Alpha	1	SA
4.4	WHO drug reference code	Alpha-numeric	11	SA
4.5	CAS code	Numeric	10	Optional
4.6	ATC code	Alpha-numeric	7	Optional
4.7	Frequency of dosing	Alpha-numeric	3	SA
4.8	Quantity per dose	Alpha-numeric	7	SA
4.9	Total cumulative dose	Alpha-numeric	7	SA
4.10	Route of administration	Alpha	2	SA
4.11	Was drug stopped?	Alpha	1	SA
4.12	Drug start date	Date	9	SA
4.13	Drug stop date	Date	9	SA
4.14	Duration of dosing	Alpha-numeric	4	SA
4.15	ICD-10 code for identification	Numeric	5	SA
4.16	Dechallenge	Alpha	2	SA
4.17	Rechallenge	Alpha	2	SA
4.18	Drug interaction suspected?	Alpha	1	SA
4.19a	Lot/batch number	Alpha-numeric	20	AF
4.19b	Expiration date	Date	9	AF
5.1	Country of notifier	Alpha	3	SA
5.2	Type of notifier (Physician, pharmacist, etc.)	Alpha	2	SA
5.3				
5.4				
5.5	Was event medically reconfirmed?	Alpha	1	SA
6.1a	Audit trail (date)	Numeric	9	SA
6.1b	Audit trail (time)	Numeric	4	SA
6.1c	Audit trail (identifier)	Alpha-numeric	9	SA
6.1d	Audit trail (comment)	Free text	200	Optional
6.2	Custodian-I re-evaluation of case	Alpha	39	Optional
6.3a	Retrieval of information (date)	Numeric	9	SA

6.3b	Retrieval of information (time)	Numeric	4	SA
6.3c	Retrieval of information (identifier)	Alpha-numeric	9	SA

* Field type; SA=shared electronic area; AF= available field (not shared area)

Appendix 2

SAMPLE REPORT ONLY

CIOMS

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH (Day / Month / Year)	2a. AGE	3. SEX	4-6. REACTION ONSET (Day / Month / Year)	8-11. CHECK ALL APPROPRIATE TO ADVERSE REACTION:
KG	USA	23 / JAN / 1913	81 YRS	FEMALE	26 / NOV / 1994	☐ PATIENT DIED ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

7+13. DESCRIBE REACTION(S) *(Including relevant tests/laboratory data)*

EXANTHEMA

This 81 year old female was treated with ANTIBIOTIC X from 24NOV94 to 26NOV94 due to bronchitis. On 26NOV94 she developed generalized exanthema. Hospitalization and treatment with cortisone were necessary.

II. SUSPECT DRUG INFORMATION

14. SUSPECT DRUG(S) *(Include generic name)*

ANTIBIOTIC X (GENERIC NAME ANTIBIOTIC X) — **ORAL** — **24NOV94:26NOV94**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ N/A ☒ UNKNOWN

15. DAILY DOSE	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
UNKNOWN	PO	☐ YES ☐ NO ☒ N/A ☐ UNKNOWN

17. INDICATION(S) FOR USE
BRONCHITIS

18. THERAPY DATES *(From:To)*	19. THERAPY DURATION
24NOV94:26NOV94	3 DAYS

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
UNKNOWN

23. OTHER RELEVANT HISTORY *(e.g., diagnoses, allergies, pregnancy with last month of period, etc.)*
UNKNOWN

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24b. MFR. CONTROL NO.
9410718

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check all that apply)*	
15DEC94	☐ Study	☐ Literature
	☒ Health Professional	☐ Registry

25. DATE OF THIS REPORT	25a. REPORT TYPE	
05JAN95	☒ INITIAL	☐ FOLLOW-UP

Appendix 3

Sample completion of data fields for electronic shared-data format (see attached CIOMS-I form)

1.1 (SA) Reference identification number

P	1	2	3	4	5	6	U	S	A	#	#	9	4	1	0	7	1	8

1.2 (SA) Country of reaction

U	S	A

1.3 (SA) Custodian -I

1	2	3	4	5	6	U	S	A

1.4 (AF) Country where drug obtained

U	S	A

1.5 (AF) Country of notifier

U	S	A

1.6a (SA) Date of first notification

1	5	D	E	C	1	9	9	4

1.6b (SA) Date last follow-up information received

1	5	D	E	C	1	9	9	4

1.6c (SA) Date received by regulator

#	#	J	A	N	1	9	9	5

1.6d (SA) Date received by WHO

#	#	J	A	N	1	9	9	5

1.7 (SA) Nature of report, not applicable in this case

N	A

Sample completion of data fields for electronic shared-data format (see attached CIOMS-I form)

1.8 (SA) Type of report (spontaneous, etc)

S

2.1 (AF) Patient identification (not to be in shared electronic area)

2.2 (AF) Patient origin (e.g., city)

2.3 a (SA) Patient age at time of reaction

0	8	1

2.3b (SA) Units for patient age

Y

2.4 (SA) Patient date of birth

2	3	J	A	N	1	9	1	3

2.5 (SA) Gender

F

2.6 (SA) Background data available (not available in this case)

N	N	N	N	N	N

2.7 (SA) Parent-Child reactions, not applicable in this case

3.1a (SA) Reaction/event date

2	6	N	O	V	1	9	9	4

3.1b (SA) Duration dosing prior to event

0	3	D	Y	C

Sample completion of data fields for electronic shared-data format (see attached CIOMS-I form)

3.2 (SA) Event term

G	E	N	E	R	A	L	I	Z	E	D		E	X	A	N	T	H	E	M	A

3.3 (SA) Serious (Y/N)/Death/Hospital/Life threatening, etc

Y	#

3.4 (SA) Labelled in product data sheet

Y

3.5 (SA) Outcome of case

O	#

3.6 (SA) Outcome of event

O

3.7 (SA) Death information; not applicable in this case

#	#	#	#	#	#	#	#	#	#	#

3.8 (SA)

Free text

"81 year old female treated with "ANTIBIOTIC X" for 3 days (24 Nov-26 Nov 1994) for bronchitis. developed generalized exanthema on 26 NOV requiring hospitalization and cortisone treatment. Further infomation currently unavailable."

4.1 (SA) Brand name of drug

A	N	T	I	B	I	O	T	I	C		X									

4.2 (SA) Generic name of drug

G	E	N	E	R	I	C		N	A	M	E		A	N	T	I	B	I	O	T	I	C		X

4.3 (SA) WHO drug reference code

#	#	#	#	#	#	#	#	#	#	#

4.4

Sample completion of data fields for electronic shared-data format (see attached CIOMS-I form)

4.5 (O) CAS code

#	#	#	#	#	#	#	#	#	#

4.6 (O) ATC code

#	#	#	#	#	#	#

4.7 (SA) Frequency dosing; unavailable in this case

#	#	#

4.8 (SA) Quantity per dose; unavailable in this case

#	#	#	#	#

4.9 (SA) Total cumulative dose; unavailable in this case

#	#	#	#	#

4.10 (SA) Route of administration

P	O

4.11 (SA) Was drug stopped?

Y

4.12 (SA) Drug start date

2	4	N	O	V	1	9	9	4

4.13 (SA) Drug stop date

2	6	N	O	V	1	9	9	4

4.14 (SA) Duration

0	3	D	Y	C

4.15 (SA) ICD code for indication

4	6	6	0	#	

Sample completion of data fields for electronic shared-data format (see attached CIOMS-I form)

4.16 (SA) Dechallenge

#	U

4.17 (SA) Rechallenge

N	A

4.18 (SA) Drug interaction

N

4.19a (AF) Lot/batch number

#	#	#	#	#	#	#	#	#	#	#

4.19b (AF) Expiration date

#	#	#	#	#	#	#	#	#

5.1 (SA) Country of notifier

U	S	A

5.2 (SA) Type of notifier (Physician, Pharmacist, Etc.)

P	H

5.3
5.4

5.5 (SA) Was report medically confirmed?

Y

6.1a, b, c (SA) Audit trail
6.2 (SA) Custodian-I re-evaluation of case

6.3a, b, c (SA) Retrieval of infromation