ETHICAL

THE SAFETY DATA (SAE) RECONCILIATION HANDBOOK

V1.3

BY ETHICAL , THE PROVIDERS OF THE eRECONCILIATION CLOUD SOFTWARE
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FOREWORD

Patient safety is the pillar of modern clinical research. Born in the aftermath of the second world war and the holocaust, Good Clinical Practice has evolved into a complex set of rules aimed at protecting the health and safety of participants in clinical studies and thus allowing us to invent, develop and provide safe and effective drugs to our customers. The collection, verification, standardization and processing of safety data is therefore a key step in the process of assessing new drugs and efforts are made to improve the way we make sure this data is complete and accurate. Information about safety data reconciliation exists but is scarce and scattered. In this handbook, clinical research professionals will find all the necessary information in one place and a practical guide on how to reconcile safety and other data collected from various sources and stored in different databases. We sincerely hope that they will find it useful. Finally, we welcome any criticism, suggestions and corrections as science always does.

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This eReconciliation handbook was compiled by Ethical GmbH, a Swiss eClinical company specialized in safety data reconciliation, endpoint adjudication, Electronic Data Capture and other data management software services for clinical research with a cumulative experience of 300 international clinical trials, over 10,000 investigator sites and hundreds of thousands of patients (www.ethicalclinical.com).

With Ethical's GxP-compliant and validated eReconciliation® software, manage all your safety data reconciliation operations easily and efficiently while improving safety data quality and validating pharmacovigilance data. (www.datareconciliation.com).

Please feel free to request your eReconciliation® FREE DEMO by emailing: mimmo.garibbo@ethical.ch.

We look forward to hearing from you.

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INTRODUCTION

All parties taking part in the conduct of clinical studies (sponsor, CRO, investigators) have obligations to report adverse events to Health Authorities (HA) and Ethics Committees (EC) / Independent Review Boards (IRB)[1,2,3,4]. In addition, sponsors are required to report on all safety issues in the Clinical Study Report (CSR) and summary documents during the application for a marketing authorization (MAA). A pharmacovigilance system must be in place to evaluate identified serious signals and, if necessary, for taking measures to minimize the risk associated with the use of the investigational medicinal products for the subjects participating in the study, including ensuring that all the parties involved (sponsors, investigators, participating subjects, regulatory bodies and members of Ethics Committees) are informed in a timely manner.

The quality of safety data collection and reporting is paramount to the establishment of the drug's safety profile and special care must be given to it. Because safety information is collected from more than one source and stored in more than one place, reconciliation of the safety data must be performed regularly during each clinical study to ensure consistency and accuracy. Occasionally, other types of data may need to be reconciled if recorded in more than one database. Data items to be reconciled may include the SAE module, the discontinuation module or the concomitant medications module. The process and tools for such reconciliation operations are common to all types of data. However, for the purpose of this handbook, we will focus on safety data pertaining to Serious Adverse Events (SAE).

2. AEs AND SAEs IN CLINICAL STUDIES

A new drug must be proven to be effective and safe in order to be granted a marketing authorization. During the development of new drugs, all adverse events, whether thought to be related to the drug or not, must be collected and presented in the Clinical Study Report (CSR). Certain categories of adverse events are categorized as "Serious" and must be followed closely until resolution. The definition of a Serious Adverse Event (SAE) is the following:

- results in deathis life threatening
- requires hospitalization, or prolongs hospitalization
- results in persistent or significant disability or defect
- is a congenital anomaly or birth defect

Medical and scientific judgment should be exercised 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 above.
These should also usually be considered serious.

Is not an AE:

- Medical or surgical procedure (However the indication leading to the procedure is an AE)
- Pre-existing diseases and condition, which do not change
- The disease being studied (lack of efficacy) might be handled differently for different indications
- Death (death is an outcome; the underlying cause is an AE)

2.1 WHY ARE AEs AND SAEs SO IMPORTANT?

Drugs contain active substances that may be beneficial if taken in certain circumstances and dangerous in others (e.g. higher dosage, prolonged use). Some effects only become apparent after prolonged use or after the drug has been used by a large number of patients. Drugs might have some anticipated risks: e.g. Amino-glycosides are known to cause ototoxicity. Drugs may have some risks of concern, e.g. almost all drugs are metabolized in the liver and hence are susceptible to drug-induced injury (Hepatic toxicity). Some risks may be missed like those occurring:

- after long-term use
- in special populations
- in association with specific diseases
- in association with concomitant therapy – in food drug interaction

All effects of drug must be studied in clinical studies and monitored during the lifetime of the drug as a marketed product.

2.2 COLLECTION OF AE / SAE

Investigators participating in clinical studies have the obligation to record in the Case Report Form (CRF) all adverse events occurring during the study and if required during a follow-up period. Adverse events collection begins at the signature of the informed consent form (ICF) by the patient. All adverse events must be collected irrespective of relation to the drug. At minimum the following elements must be provided by the investigator:

- Verbatim
- Seriousness
- Severity
- Action taken
- Relation to the drug
- Resolution

In addition, all SAE must be reported immediately (within 24 hrs.) to the sponsor – except for specific SAEs that a protocol identifies as not needing immediate reporting. A dedicated safety database (Pharmacovigilance) must be established to record the information pertaining to the SAEs.

The sponsor is responsible for the ongoing safety evaluation of the Investigational Product(s). The sponsor should promptly notify ALL concerned Investigators and the regulatory authorities of findings that could adversely affect all subjects, all impact on the conduct of the study, or alter the ethics approval/favorable opinion to continue the study.

2.3 PROCESSING OF AE/SAE DATA

CODING
Adverse events verbatim, medical history and concomitant medication are coded after collection using the MedDRA[5] dictionary of medical terms to achieve a consistency in terms allowing for classification and comparisons.

EDIT CHECKS - QUERIES
The clinical database is typically checked using automated verifications (edit checks). In case of discrepancy between different related data, a query is issued and transmitted to the investigator. Depending on the answer, data may be corrected or completed.

FOLLOW-UP

In the safety database, all SAE cases are followed up until final resolution (or lost-to-follow up) or judged to be no longer clinically significant. This process may extend past the end of the clinical study and the lock of the clinical database.

2.4 REPORTING AND DISPLAYING OF AE / SAE

REPORTING
While all adverse events must be recorded during a clinical study and presented in the CSR, only certain types are reported in an expedite manner.

During Clinical Studies, the following are reported:

- Suspected Unexpected Serious Adverse Reactions (SUSARs)- report within 7 days
- Annual Safety Report (ASR)
    - New format: Development Safety Update Reports (DSUR)
- Investigator's Brochure (IB) – Update
    - At least once per year according to Good Clinical Practice
    - Include any relevant new (including safety related) data on IMP
- Non-serious Adverse Events and/or Laboratory Abnormalities
    - Only if identified as critical safety information in the study protocol

For Marketed Products, a report is produced annually:

- Periodic Safety Update Report (PSUR)

REPORTING TIMELINES FOR SAE

From the investigator:

- to sponsor: within 24 hrs. everywhere

From the sponsor to regulatory authorities:

- for US: 15 working days

For SUSAR (Suspected Unexpected Serious Adverse Reaction):

- within 7 days & follow up report in next 8 days
- in case of death immediately (within 48 hrs).

DISPLAY IN CLINICAL STUDY REPORTS

All Clinical Study Reports (CSR) must list the observed AEs and classify them (e.g. by type, body system etc.) Serious Adverse Events and Adverse Events of Special Interest (AESI) are presented separately and described in detail in the Safety Narratives section. A written narrative must be prepared for each event detailing patient characteristics, event timing, severity and relation to the drug, actions taken and resolution. Death Listings and SAE listings are also submitted to regulatory agencies as the appendices to Clinical Study Report (CSR Appendices: 16.2 and 16.3). These reports and listings are generated from both databases (It is therefore important that the SAE data in both databases be consistent).

PUBLIC DISCLOSURE

Sponsors are strongly encouraged to publish all new clinical studies in public databases (e.g. ClinicalTrials.gov) to allow more transparency and to invite patients to participate and benefit from the latest innovations. Public databases also display summary information about the adverse events occurring during the studies.[6]

DESCRIPTION IN SCIENTIFIC PUBLICATIONS

Many clinical studies are eventually published in peer-reviewed scientific journals. These publications also report the rates and other summary information on the adverse events occurring during the study. Some authors have compared the rates reported in scientific publications to those shown in public databases and found significant differences[7].

3. SAFETY DATA RECONCILIATION

3.1. WHAT IS SAFETY DATA RECONCILIATION?

SAE data reconciliation is the process of reconciling the clinical database (i.e. Data collected on the CRF) with the Pharmacovigilance database (i.e. SAE forms) to ensure the data is consistent and not contradictory.

Reconciliation is an iterative process that usually occurs several times during the study.

Timing for reconciliation is determined by the frequency of data receipt, scheduling of safety updates, and timing of interim and final reports.

3.2. REASONS TO RECONCILE SAFETY DATA

There are several reasons why a reconciliation between the clinical and the safety database is important.

MISSING SERIOUS ADVERSE EVENTS

It is possible that one or more SAEs failed to be captured in one of the two databases. More rarely, an SAE may be missing from BOTH databases. It is advised to perform a search using keywords such as “death” or “hospitalization” to identify SAEs that may have been misclassified as non-serious.

DIFFERENCES

The most frequent case is differences in the information recorded in the two databases. This may be due to a transcription error, to corrections made after the initial reporting following a query or to follow up information received at a later time. The clinical database is usually cleaned on an ongoing basis using automated edit checks and queries to the investigator. However, this database is locked at a certain point while the pharmacovigilance database continues to collect information on all SAEs until final resolution. Discrepancies may emerge from these operations and need to be reconciled.

INCOMPLETE INFORMATION

Finally, information may be incomplete in one of the other databases. A close comparison allows to fill any existing gaps and strengthen the quality of both data sets.

3.3. SCOPE OF THE SAFETY DATA RECONCILIATION

Reconciliation may occur at several levels.

STUDIES

Safety data reconciliation must be performed for every clinical study to ensure completeness and consistency of the safety information.

EVENTS

Typically, all data pertaining to Serious Adverse Events and captured in both the clinical and the safety database are reconciled. However, other events of interest may also be reconciled if recorded in more than one place.

DATA

The data usually reconciled include but are not limited to:

- Subject ID and randomization number (if applicable)
- SAE verbatim
- LLT term
- PT term
- SOC
- Onset date
- Stop date
- Outcome
- Severity
- Seriousness criteria
- Causal relationship with study drug/ medical device
- Action taken with study drug/medical device

Additionally, data pertaining to the demographics (e.g. age, date of birth, weight, height, gender and race), to vital signs / physical examination, concomitant medication (e.g. medication, indication, start date and stop date or if ongoing) and study drug administration (e.g. study drug administration dates, batch number if applicable) can be chosen for reconciliation.

3.4. HOW TO PERFORM SAFETY DATA RECONCILIATION

There are several ways to perform data reconciliation. A manual process may be sufficient in some cases but can be time consuming and error prone. In any case, the process must be clearly described in quality documentation.

STANDARD OPERATING PROCEDURE (SOP)

A Standard Operating Procedure (SOP) must be written describing the scope, roles and responsibilities and high-level process for reconciliation. Data Management is usually responsible for producing such SOP.

DATA MANAGEMENT PLAN (DMP)

The DMP must detail the key safety data to be reconciled, the differences that may be acceptable and the cut-off point where the process will stop.

PLAN

It is advisable to prepare a detailed plan describing which data will be reconciled and the timing for reconciliation (periodic during the trial, at the end).

The team responsible for SAE Reconciliation must determine how frequently the SAE data will need to be reconciled. The interval between rounds must be based on:

- The complexity of the protocol
- Data loads or subject visits
- Subject enrollment
- The frequency of reported SAEs in both Databases
- Other Milestones
- Other timelines including database lock

PROCEDURES

The reconciliation procedure can be organized in four steps:

- Retrieve data from the two databases
- Information checking
- Corrective actions
- Process Tracking

GUIDELINES

Each sponsor may issue guidelines to help consistency and productivity of the reconciliation process.

3.5. WHO IS INVOLVED IN SAFETY DATA RECONCILIATION?

The two departments typically involved in safety data reconciliation are Drug Safety / Pharmacovigilance and Clinical Data Management.

SPONSOR/ CRO

The sponsor is responsible for the complete and accurate reporting of safety information. A sponsor may be represented by a CRO and delegate such responsibility. Sponsors must put in place all the necessary tools to ensure the highest quality of data including a reconciliation process.

DATA MANAGER

Data managers are responsible for the quality and completeness of the clinical database. They collaborate with Drug Safety and if needed with IT to ensure the reconciliation with the safety database of key SAE information.

IT MANAGER

If computer tools are used for the reconciliation, IT may be involved to validate and maintain those tools. If the service is provided by an external entity as SaaS, IT may be involved in contracting.

SAFETY OFFICER

The safety officer is the custodian of all safety data and must collaborate with Data Management to set up the reconciliation process.

MONITOR

Clinical monitors are in close contact with the investigational sites for the collection of both clinical and safety data and may be involved in query resolution and corrections.

MEDICAL OFFICER

The medical officer is responsible for the periodic safety review during the study. They may be instrumental in the detection of SAEs and in the resolution of discrepancies.

PRINCIPAL INVESTIGATOR

The principal investigator is responsible for providing all initial information as well as updates, answer queries and liaise with other healthcare providers who may have been involved in an SAE.

3.6. TIMING FOR SAFETY DATA RECONCILIATION

Periodic reconciliation has value only if the data is being updated in both databases on a frequent basis. If the Safety database is not updated on a timely basis, frequent reconciliation will be counterproductive. Also, if the queries are not answered quickly by the site, and there is a high number of outstanding queries from the previous round of reconciliation, frequent rounds of reconciliation cannot be productive.

4. PROCEDURES: e-RECONCILIATION IN 10 EASY STEPS

Below is a practical guide to data reconciliation based on the information given in the previous chapters and on a long practical experience of the authors:

Step 1: Carefully select your clinical data collection tools (EDC / eCRF) and safety information collection tools (Pharmacovigilance). Some of these tools are integrated and allow for easier reconciliation. However, this must be weighed against other advantages and disadvantages of each system.

Step 2: Prepare the DMP: Define upfront the events and data that will need to be reconciled and check if the coding is consistent in the two databases. This will greatly help when reconciliation time comes. Define the acceptable differences and the cut-off point.

Step 3: Review any existing SOP, Guidelines and determine if updates are needed. All roles and responsibilities must be clearly stated before the start of the clinical study.

Step 4: Define the frequency of the reconciliation as well as the actions to be performed after each round of reconciliation (queries issue, data correction, re-run...).

Step 5: Train all participants in the process and document training in the Trial Master File (TMF)

Step 6: After the start of the trial, run a test round using the first SAEs to check the process and the tools. Involve all roles including the safety officer and the medical officer to ensure that everyone understands their respective roles.

Step 7: Run periodic reconciliation rounds according to the plan and perform the necessary actions to correct discrepancies. If needed, make team decisions on any changes in the process and document these in the TMF.

Step 8: At the cut-off point, perform one final reconciliation round to make sure all data has been reviewed.

Step 9: Perform a search for missing SAEs / AESI using keywords to ensure completeness of the safety information. If missing events are found, request recording and reconcile.

Step 10: Document the results of the reconciliation and file the documentation in the TMF.

5. SOFTWARE & DATA MANAGEMENT

What about the software? Should reconciliation be done manually, using spreadsheets, semi-manually with the use of software tools or can it be totally automated? If you should use software, make sure that Data Management and IT are involved and that any tools used can easily be interphased to the EDC and Pharmacovigilance databases.

5.1. SOFTWARE REQUIREMENTS

SOFTWARE VALIDATION (ACCEPTANCE TESTS)

Before accepting the system for regular use, the users must verify the fulfilment of all and each user requirements (traceability matrix) by testing the relevant functions using test scripts and documenting the successful completion in a summary report.

SOFTWARE TRAINING

Compliance of validated systems is not limited to functional capacities (the system can do the required operations) but is also dependent on appropriate training (the users know how to operate the system correctly) and acknowledgement (the users understand the meaning and consequences of using the system). Appropriate training material must be prepared, and training delivered and documented before access is granted.

SOFTWARE INTEGRATION

Data reconciliation platforms perform optimally when integrated with other data processing systems such as EDC and Pharmacovigilance.

6. GLOSSARY

Adverse drug reaction (ADR):

- During pre-approval clinical experience: All noxious and unintended responses to a medicinal product related to any dose.
- For marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

  (Source: ICH)

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (source: ICH))

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (source: ICH)

Adverse event of special interest (AESI): Adverse events defined by the sponsor as being of special interest in the framework of a given clinical study. These are usually reported separately and a dedicated narrative is presented in the Clinical Study Report (CSR) alongside the Serious Adverse Events narratives.

Case Record/Report Form (CRF): A printed, optical, or electronic document (eCRF) designed to record data on each trial participant during the course of the trial as defined by the protocol. The data should be collected by procedures, which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Clinical Data Management System (CDMS): The system used in a clinical trial to manage the data.

Contract Research Organization (CRO): a person or an organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Clinical Study Report (CSR): A written description of a trial/study of any therapeutic, prophylactic or diagnostic agent conducted in human subjects in which the clinical and statistical description, presentations, and analyses are fully integrated in a single report.

Data Correction Request Form (DCRF) or data clarification form (DCF): The official communication form using a standard query text to the investigative site for clarification of an SAE data variable and to document any changes to data already captured in the clinical database.

Data Management Plan (DMP): A document describing the process that will be followed for the processing and management of clinical data during a clinical study.

IT: Information Technology (usually means the IT department).

MedDRA: Medical Dictionary for Regulatory Activities (MedDRA) coding data into a standardized international medical terminology to facilitate its analysis.

Query: Question sent to an investigative site to clarify an SAE data variable. A query is managed using a DCF.

Safety database: The database used by safety groups to process and manage SAE data from clinical trials and marketed products. SAE reports (or "cases") entered in the safety database are updated as follow-up information becomes available. Examples of safety databases include: ARGUS, ARIS-G, AERS, SAFIRE.

Clinical database: The database used by clinical teams to collect and file clinical data during the life of a clinical trial, including the SAEs occurring during the clinical trial. Examples of clinical databases include: RAVE, InFORM, ORACLE CLINICAL.

Serious adverse event or reaction (SAE or SAR): Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. 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.

(source: ICH)

SAE data reconciliation: The process of comparing key safety data variables between the drug or device safety SAE database and the clinical database in order to identify any discrepancy, determine whether a discrepancy is acceptable or not and, if acceptable, document the discrepancy. It is an iterative process that occurs several times during the study. When to reconcile is determined by the frequency of data receipt, scheduling of safety updates and timing of interim and final reports. The objective is to reconcile all discrepancies before final clinical database lock in order to submit validated data to regulatory authorities.

SAE discrepancy: A mismatch between the safety database and the clinical database identified during the reconciliation process. A discrepancy can be for example:

- An SAE present in one database but missing in the other one
- Inconsistent SAE associated data between the databases
- Missing SAE associated data in one of the databases
- Mismatched SAE preferred term

All the identified discrepancies, actions taken to address the discrepancies, and the status relevant to the action taken are recorded in the SAE manual or electronic reconciliation tool.

SAE reconciliation listing: File listing, generally in Excel format, used to review and document all discrepancies, acceptable or not, found during SAE data reconciliation.

Serious adverse event (SAE) report form: Form used to report an SAE. An SAE report form contains information such as the event onset date, date that it became serious and end date, seriousness criteria (resulted in death, was life-threatening, required hospitalization, etc.), the severity (e.g.: mild, moderate, severe), the outcome (fatal, not resolved, resolved, resolved with sequelae, resolving, unknown), suspected drug(s) information and a causality assessment. (see also SAE reporting regulations).

Suspected unexpected serious adverse drug reaction (SUSAR): A serious adverse reaction (SAR) for which a reasonable causal relationship with the medicine used is suspected but not confirmed. Unexpected means not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary for an approved product).

Trial Master File (TMF): The collection of the essential documents of a trial which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. TMSs are established at the beginning of the trial, both at the investigator's site and at the sponsor's office and are updated with new relevant documents as new information becomes available.

Unexpected adverse drug reaction (UAR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary for an approved product). (source: ICH)

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