Seminário Farmacovigilância:
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Overview of ICH E2B(R3)

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Basis of E2B Transmission

Agenda

- What is E2B transmission and the advantages
- Summary of ICH E2B guideline
- Methods of E2B transmission
- Differences between R2 and R3
- Technical and procedural pre-requisites for E2B implementation
- Language of case notification and MedDRA
- Business continuity plan for E2B transmission
- Data protection

Basis of E2B Transmission

Agenda

- A brief history of E2B
- The business case for electronic reporting
- Summary of ICH E2B(R3) Guideline
- Essential Components of E2B(R3) Messages
- Regional Implementation Guide
- Implementation Planning

A Brief History of E2B

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A brief history of E2B

First introduced in 1997, the E2B standard has undergone several revisions

Date	Description	Original Naming	Updated 2005 Naming
17Jul'97	Initial version step 4 approval	E2B	E2B
10Nov'00	First revision approval	E2B(M)	E2B(R1)
05Feb'01	Editorial corrections (second revision)	E2B(M)	E2B(R2)
12May'05	Approval of the third revision by the Steering Committee under Step 2 and release for public consultation.	E2B(R)	E2B(R3)
Nov 2012	Version 5.0 reaches step 4 - no publication	N/A	E2B(R3)
April 2013	V5.01 – Step 4 – Editorial corrections prior to publication	N/A	E2B(R3)
Nov 2016	V5.02 – Step 4 – Editorial changes based on QA	N/A	E2B(R3)

A brief history of E2B – Q&A

E2B has maintained frequently asked questions to aid implementers

Date	Description	Original Naming	Updated 2005 Naming
18Jul'03	Approval of version 0.2	E2B(M) Q&A's	E2B Q&A's
11Nov'03	Approval of version 0.3	E2B(M) Q&A's	E2B Q&As(R1)
10Jun'04	Approval of version 0.4	E2B(M) Q&A's	E2B Q&As(R2)
18Nov'04	Approval of version 0.5	E2B(M) Q&A's	E2B Q&As(R3)
07Jan'05	Approval of version 1.0	E2B(M) Q&A's	E2B Q&As(R4)
03Mar'05	Approval of version 1.1	E2B(M) Q&A's	E2B Q&As(R5)

A brief history of E2B

Development of E2B(R3)

- Prior to E2B(R3), ICH electronic messaging standards were developed by the ICH M2 EWG for Electronic Standards for the Transmission of Regulatory Information(ESTRI).
- E2B(R3) is an international standard developed through a partnership with external (to ICH) Standards Development Organisations (SDOs)
- Current E2B(R3) message standard was developed through a collaborative relationship between the ICH and the Joint Initiative Council (JIC); the JIC is a partnership of the International Organisation for Standardisation (ISO), the Health Level Seven (HL7), the European Committee for Standardisation (CEN), the Clinical Data Interchange Standards Consortium (CDISC), the International Health Terminology Standards Development Organisation (IHTSDO), and GS1*

*GS1 is an international not-for-profit association dedicated to the design and implementation of global standards and solutions to improve the efficiency and visibility of supply and demand chains globally and across sectors.

A brief history of E2B

Development of E2B(R3)

- Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR' is available at the ISO website (http://www.iso.org/iso/store.htm). The ICSR standard named 'ISO / HL7 27953-2: 2011

The Business Case for Electronic Reporting

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Advantages of E2B Transmissio

The business case for electronic ICSR exchange

Historically, the exchange of safety information was based on paper-based formats (e.g. Yellow Cards, CIOMS I forms, MedWatch forms, etc.) or electronic media (e.g. on-line access, tape, CD, etc). Considering the large number of potential participants in a world-wide exchange of information, there should be a standard format that is capable of accommodating direct database-to-database transmission using standardised message transfers. Successful electronic transmission of information relies on the consistent and uniform interpretation of definitions for common data elements and standard transmission procedures.

Source: ICH ICSR Implementation Guide, 10 November 2016

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Advantages of E2B Transmissio

The business case for electronic ICSR exchange

Over the last decade as the number of case reports has increased, exchange of ICSRs has increasingly shifted from paper-based to electronic reports and electronic transmission of case safety information has become an important component of global pharmacovigilance. The ICH released a consensus electronic standard for ICSRs in 1997 and this standard has undergone a number of revisions since it was first adopted. The ICH E2B(R2) standard has been used for regulatory compliance purposes for several years and, indeed, is now mandatory in some ICH regulatory jurisdictions and is widely accepted.

Source: ICH ICSR Implementation Guide, 10 November 2016

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Advantages of E2B Transmissio

The business case for electronic ICSR exchange

Because of national and international agreements, rules, regulations, and the protection of patient safety, there is a need to expedite the exchange of safety information (e.g. ICSRs):

- from identified reporting sources to regulatory authorities and pharmaceutical companies;
- between regulatory authorities;
- between pharmaceutical companies and regulatory authorities;
- between pharmaceutical companies;
- from clinical investigators, via the sponsor of a clinical trial, to ethics committees; or
- from authorities to the World Health Organisation (WHO) Collaborating Centres for International Drug Monitoring

Source: ICH ICSR Implementation Guide, 10 November 2016

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Advantages of E2B Transmissio

The business case for electronic ICSR exchange

The ICH ICSR enhances electronic adverse event reporting and analysis by facilitating the efficient reporting of suspected product-related adverse events/reactions. The electronic environment:

- improves the ability to efficiently exchange and process ICSR data;
- facilitates the transfer of information to organisations who need it;
- enables incoming messages to be automatically routed and processed;
- facilitates aggregation of safety data for analysis; and
- allows minimising resources required for data (re-)entry activities.

Source: ICH ICSR Implementation Guide, 10 November 2016

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Summary of ICH E2B(R3) Guideline

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What is ICH E2B?

E2 is the family of ICH efficacy guidelines supporting pharmacovigilance

E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

- The tripartite harmonised ICH Guideline was finalised under Step 4 in October 1994. This document gives standard definitions and terminology for key aspects of clinical safety reporting. It also gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

E2B(R3) – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

Source: ICH Website: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

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What is ICH E2B?

E2 is the family of ICH efficacy guidelines supporting pharmacovigilance

E2B(R3) IWG – Implementation: Electronic Transmission of Individual Case Safety Reports

- In July 2013, the ICH Steering Committee endorsed the establishment of the IWG on E2B(R3) to assist with the implementation of the E2B(R3) Implementation Guide (published in July 2013) and help facilitate transition from E2B(R2) to E2B(R3). Included in its tasks is support for the use of constrained ISO IDMP terminologies in ICSRs, as well as maintenance of technical documents related to E2B(R3).
- In November 2014, the IWG finalised the first version of Questions & Answers (Q&As) to clarify questions and comments for E2B(R3) implementation, the group will continue updating the Q&As to address new questions and comments

Source: ICH Website: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

What is ICH E2B?

E2 is the family of ICH efficacy guidelines supporting pharmacovigilance

The overall E2B standard is based upon an HL7 ICSR model that is capable of supporting message exchange for a wide range of product types (e.g. human medicinal products, veterinary products, medical devices etc.) The framework is described in:

- ISO/HL7 27953-1: 2011 Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 1: The framework for adverse event reporting

The second part of the standard, which is a subset of the ISO/HL7 27953-1:2011, defines the details of the reporting requirements for human pharmaceuticals :

- ISO/HL7 27953-2: 2011 Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR

The standards mentioned above reached International Standard status in November 2011 and were published jointly by ISO and HL7.

Source: ICH ESTRI Website: http://estri.ich.org/e2br3/index.htm

What is ICH E2B?

E2 is the family of ICH efficacy guidelines supporting pharmacovigilance

ICH constrained the ISO ICSR standard to meet the data exchange requirements for E2B(R3). ICH defines the way that this standard should be used by means of the ICH Implementation Guide (IG) which covers the use of the fields defined by E2B(R3). The ISO standard itself does contain additional data elements or requirements that are not used by ICH but may be used by specific regions. Such use, where appropriate, will be defined by regional Implementation Guides.

Please ensure that, when using the ISO/HL7 standard for ICSR, the following version is used: "ISO/HL7 27953-2:2011Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR". Do not use other versions of the standard since they might include changes that are not relevant for the submission of ICSRs in the regulated biopharmaceutical domain.

Source: ICH ESTRI Website: http://estri.ich.org/e2br3/index.htm

What is ICH E2B?

Contents of ICH Implementation Guide (IG) Package – Version 1.07, June 2018

Contents of the E2B(R3) Implementation Guide
0_Summary of document history_v1_6.pdf
1_ICH_ICSR_Imlementation_Guide_v5_02.pdf
3_ICH_ICSR_BFC – Support backwards/forwards conversion between E2B(R2) and E2B(R3) • 3_BFC Element Mapping v2_02.xls • 3_ICH_ICSR_BFC_Specification_v2_02.pdf
4_ICH_ICSR_Schema_Files – See Appendix I (Preparing and Sending ICH ICSRs) in the E2B(R3) IG for further details on ICH ICSR schemas
5_Reference_Instances – Sample of ICSR and ICSRACK messages in E2B(R3) format
6_Example_Instances – Examples of specific reporting scenarios in both XML and Excel in E2B(R3) format

Source: ICH ESTRI Website: http://estri.ich.org/e2br3/index.htm

What is ICH E2B?

Contents of ICH Implementation Guide (IG) Package – Version 1.07, June 2018

Contents of the E2B(R3) Implementation Guide
7_E2B Bilingual Code Lists v2.9 – Code lists and related object identifiers (OIDs) used in the ICH E2B(R3) Implementation Guide
8_Technical Information – Technical information (datatypes, etc.) to facilitate the preparation of a valid ICH ICSR message, or an ICSR Acknowledgment Message for electronic submission. Useful for IT teams implementing E2B(R3).
9_EU BFC_conversion_v.2.5.zip – Additional information on implementing BFC in the EU region
10_User_Guide_Dose_Forms_and_Routes_of_Administration_v1_0.pdf – Use of EDQM terminologies for Dose Forms and Routes of Administration in E2B(R3)
11_ICH E2B(R3) Core Data Elements and Business Rules ver.1.00.xslx – Common template that summarises the core ICH E2B(R3) data elements, business rules and any associated questions and answers. Updated regionally.

Source: ICH ESTRI Website: http://estri.ich.org/e2br3/index.htm

What is ICH E2B?

E2B(R3) Questions and Answers

E2B(R3) Questions and Answers
Document History Q&A_v1_2.pdf • Change history for Q&A document
ICH E2B(R3) QA document_v2_2.pdf • Clarifications for the harmonized interpretation of the E2B(R3) IG package and should be reviewed in conjunction with the IG package

Pharmaceutical companies, regulators and vendors are encouraged to submit implementation-related questions to the ICH E2B(R3) EWG/IWG; answers to these questions are developed by the ICH E2B(R3) EWG/IWG in accordance with the ICH consensus process.

Source: ICH ESTRI Website: http://estri.ich.org/e2br3/index.htm

Essential Components of E2B(R3) Messages

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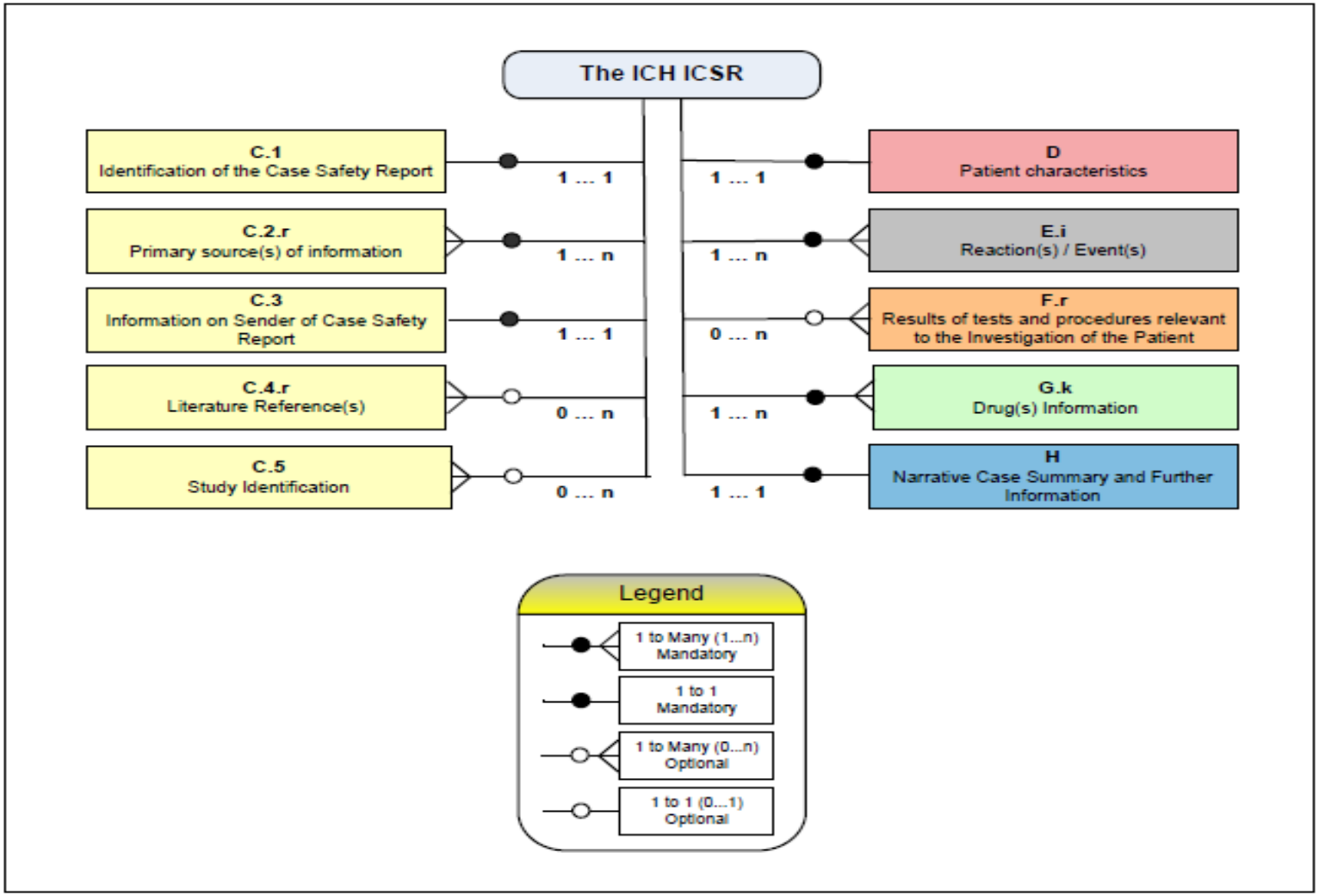
ICH ICSR Relational Diagram



Source: ICH ICSR Implementation Guide, 10 November 2016

Code Sets, Terminologies and Vocabularies for E2B(R3)

- There are several terminologies and controlled vocabularies that are used to describe or code information within an ICSR.
- Some of these terminologies or code sets are general and are used by many applications, such as units for mass or time, or country codes.
- Some are specific to the medical section – MedDRA – Medical Dictionary for Regulatory Activities
- Some are specific code lists created for ICH use.

- Code list maintenance is the responsibility of the 'Maintenance Organization' that developed the list and should be consulted for the most up to date version of the code list
- Object Identifiers (OIDs) are used to distinguish namespaces or intended use of data elements

Source: ICH ICSR Implementation Guide, 10 November 2016

Terminologies and Vocabularies

ISO Identification of Medicinal Products (IDMP)

In collaboration with ICH, ISO developed a set of standards to enhance exchange of information for medicinal products.

- ISO 11238 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances
- ISO 11239 Health Informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
- ISO 11240 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement
- ISO 11615 Health Informatics —Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated medicinal product information
- ISO 11616 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

Source: ICH ICSR Implementation Guide, 10 November 2016

Terminologies and Vocabularies

MedDRA - Medical Dictionary for Regulatory Activities

- Medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g. medical devices and vaccines).
- Developed by ICH, MedDRA trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.
- The MSSO - Maintenance and Support Services Organization - serves as the repository, maintainer, and distributor of MedDRA as well as the source for the most up-to-date information regarding MedDRA and its application within the biopharmaceutical industry.
- The ICH ICSR utilises MedDRA to code a number of medical concepts, such as adverse reactions or events, indications for drug use, medical history, etc.
- MedDRA is updated twice per year and only one version of MedDRA can be used in a single ICSR.

Source: ICH ICSR Implementation Guide, 10 November 2016

Terminologies and Vocabularies

International Standard Code Sets

Information on Code Sets and OIDs relevant to this IG but not specifically created by or for ICH.

- These code sets are maintained internationally in various places by organisations and entities other than ICH.
- ISO 3166 Part 1 (alpha-2) —Codes for the representation of names of countries and their subdivisions— Part 1: Country codes, defines codes for the names of countries, dependent territories, and special areas of geographical interest (2-letter codes)
- ISO 5218 —Information technology —Codes for the representation of human sexes
- ISO 639-2 —Codes for the Representation of Names of Languages
- UCUM — The Unified Code for Units of Measure (UCUM), case sensitive form

Source: ICH ICSR Implementation Guide, 10 November 2016
More information on UCUM at http://unitsofmeasure.org/
The UCUM standard can be downloaded in xml or html form from http://unitsofmeasure.org/trac/

Specifications for ICSR Transmission

General Principles

All the information available should be reported in fully structured format using the relevant E2B(R3) data elements and applicable standard terminologies.

While complete information is desirable, a minimum set of information is always required for an ICSR to be valid. This applies to all types of ICSRs including initial case reports, follow-up information, and cases to be amended or nullified

Although the exchange of other unstructured data (e.g. published articles, full clinical records, X-Ray images, etc.) is outside the scope of the IG, the technical solution to transmit attachments is provided

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Minimum Information

The minimum information for valid safety report should include at least:

- one identifiable patient - any one of several data elements is considered sufficient to define an identifiable patient (e.g. initials, age, sex);
- one identifiable reporter - any one of several data elements is considered sufficient to define an identifiable reporter (e.g. initials, address, qualifications);
- one adverse event/reaction (or outcome); and
- one suspect or interacting drug.

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Data Elements within a Message

In addition to the minimum information required for an ICSR report, certain specific administrative information should be provided to properly process the report:

- Sender's (case) Safety Report Unique Identifier (C.1.1);
- Type of Report (C.1.3);
- Date of Most Recent Information for This Report (C.1.5);
- Dose This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7);
- Worldwide Unique Case Identification (C.1.8);
- Reporter's Country Code (C.2.r.3);
- Sender's Organisation (C.3.2); and
- When type of report='Report from study', Study Type Where Reaction(s) / Event(s)Were Observed (C.5.4).

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Retransmission

Based on regional reporting obligations and business arrangements in pharmacovigilance, an ICSR may be re-transmitted several times between different senders and receivers.

During this re-transmission process, medical information ‘received’ on the case should not be omitted or changed during the retransmission when no new information on the case is available to the re-transmitting sender.

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Retransmission – Exceptions for updating Data Elements

- Sender's (case) Safety Report Unique Identifier (C.1.1);
- Date of Creation(C.1.2);
- Date Report Was First Received from Source (C.1.4);
- Date of Most Recent Information for This Report (C.1.5);
- Are Additional Documents Available? (C.1.6.1);
- Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7);
- More Information Available (F.r.7);
- Information on Sender of Case Safety Report (C.3);
- Seriousness Criteria at Event Level (E.i.3.2);
- Assessment of Relatedness of Drug to Reaction(s)/ Event(s) (repeat as necessary) (G.k.9.i.2.r);
- Sender's Diagnosis (repeat as necessary) (H.3.r);
- Sender's Comments (H.4); and
- English translation of the free text data elements in the ICSRs.

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Data Element Format

Section A

- C.1 - Identification of the Case Safety Report;
- C.2- Primary Source(s) of Information;
- C.3 - Information on Sender of Case Safety Report;
- C.4 - Literature Reference(s);
- C.5 - Study Identification.

Section B

- D – Patient Characteristics;
- E - Reaction(s)/ Event(s);
- F - Results of Tests and Procedures Relevant to the Investigation of the Patient;
- G - Drug(s) Information; and
- H - Narrative Case Summary and Further Information.

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

General Rules on Data Entry

Date / Time Format

- HL7 uses a single format to represent dates and times; Complete date time information down to seconds can be reported using this format

Free Text

- Provided in English for International Transmission
- Exceptions:
  - Reaction/Event as Reported by the Primary Source in Native Language' (E.i.1.1a)
  - 'Case Summary and Reporter's Comments in Native Language' (H.5.r)
- Message control act wrapper supports language codes for regional message exchanges

Metric units only

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

General Rules on Data Entry – NULL Values / nullFlavors used in E2B(R3)

Code	Name	Definition
NI	No Information	No Information
MSK	Masked	Available but not provide (ie, data privacy)
UNK	Unknown	Value not known
NA	Not Applicable	No applicable value
ASKU	Asked, unknown	Information sought, but not found
NASK	Not asked	Information not sought
NINF	Negative Infinity	Negative infinity of numbers
PINF	Positive Infinity	Positive infinity of numbers

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Document Attachments

Embed attachments into the structure of the ICSR XML message. Providing a hyperlink to the document stored separately is not acceptable.

Each attachment has up to 3 properties, and the appropriate value for each property should be provided in either C.1.6.1.r.2 or C.4.r.2:

- Media Type: Identifies the type of the encapsulated data and identifies a method to interpret or render the data. This property indicates the data type standardised by RFC 2046 (http://www.ietf.org/rfc/rfc2046.txt), (e.g. application/PDF, image/jpeg, application/DICOM).The default value for media Type is text/plain.
- Representation: Presents the type of the encapsulated data. Use TXT for text data or B64 for binary data encoded by Base 64.
- Compression: Indicates whether the data is compressed, and what compression algorithm was used (e.g. value DF means the deflate algorithm was used).

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

Amendment Reports

E2B(R3) provides data elements used to indicate that a previously transmitted ICSR is either considered completely void (nullified) (for example when the whole case was found to be erroneous), or amended (for example when, after an internal review or according to an expert opinion, some items have been corrected, such as adverse event/reaction terms, seriousness, seriousness criteria or causality assessment).

The date originally reported in C.1.5 (Date of Most Recent Information for This Report) should not be changed in an amended or nullified report if no new information on the case has been received.

Source: ICH ICSR Implementation Guide, 10 November 2016

Specifications for ICSR Transmission

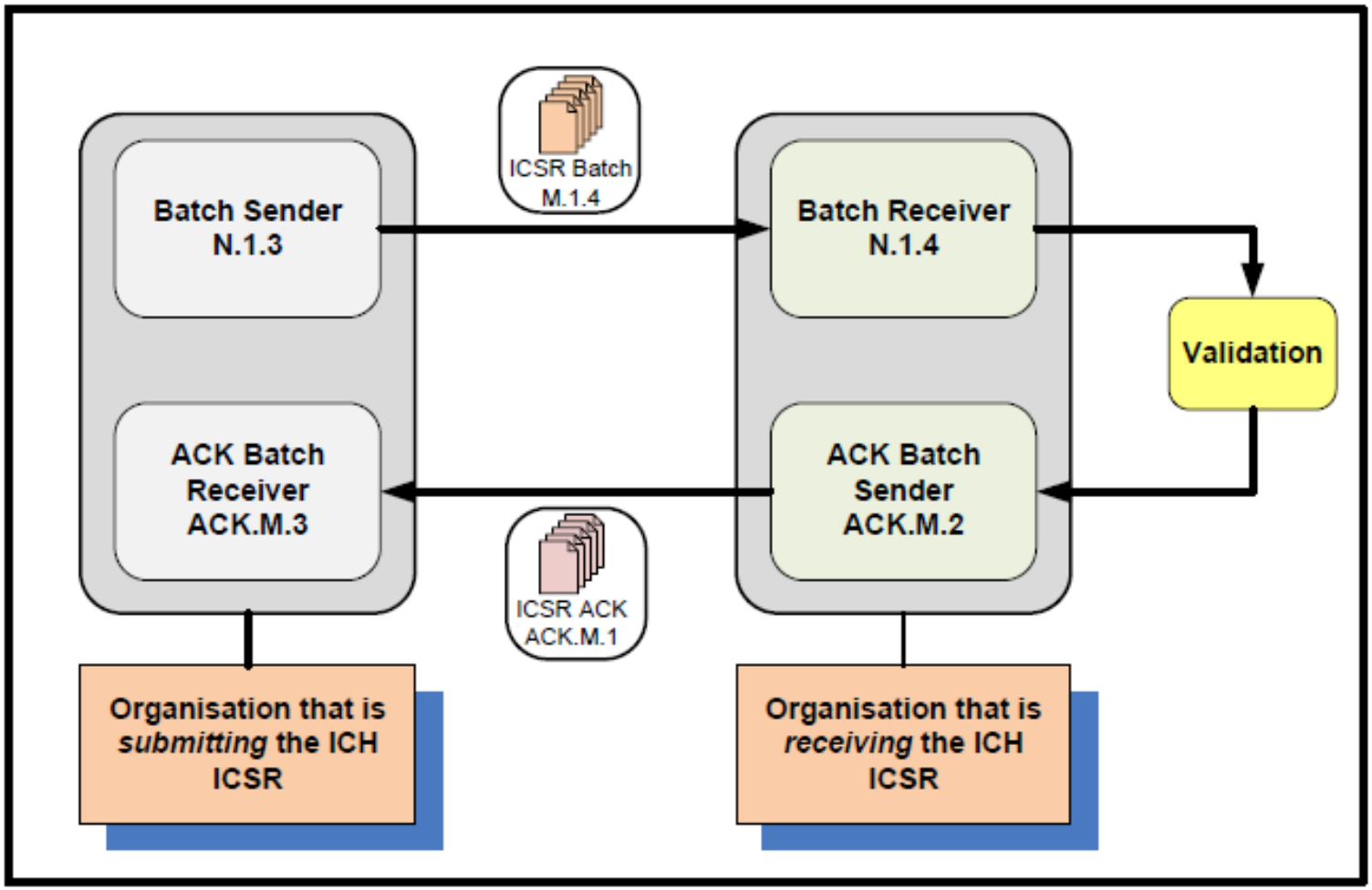
ICSR Acknowledgements

An acknowledgment transaction will be sent after receipt of every ICH ICSR from known trading partners (information received from unauthorized or unknown trading partners is not acknowledged).The acknowledgement message includes a standard ICH ICSR header, an acknowledgment for the message, and a repeating details section that provides information about the processing of the original message, e.g. successful parsing or problems that prevented parsing/accepting the message.

It is important to note that the ICH ICSR Acknowledgement is structured as the response to a **batch message**, and that it contains information both for the batch and for individual messages (reports) within that batch.

Source: ICH ICSR Implementation Guide, 10 November 2016

ICSR Transmission and Acknowledgement



Source: ICH ICSR Implementation Guide, 10 November 2016

Regional Implementation Guide

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Regional Implementation Guides

Region specific requirements for electronic submission

The ICH E2B(R3) Implementation guide was developed through international harmonisation using a consensus approach.

The majority of the requirements of the three ICH regions were able to be incorporated in to the ICH E2B(R3) IG however some additional requirements due to differences in regional legislation could not be covered

The ICH E2B(R3) IG makes provisions for this fact and it is expected that each ICH region will produce its own regional IG based on the core set of the ICH document

The intention is that each region's IG will not conflict with each other

Regional Implementation Guidelines specify technical requirements and the process for transmitting ICSRs and ICSR Acknowledgements and describes the obligations of stakeholders in ensuring successful electronic communication

Source: EU ICSR Implementation Guide, July 2017

Regional Implementation Guides

Electronic Data Interchange

Regional IG should describe the procedures concerning the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs)

The procedures should ensure:

- the protection of Safety and Acknowledgement Messages against the risks of unauthorised access, disclosure, alteration, delay, destruction or loss, ensuring the verification of integrity, the nonrepudiation of origin and receipt and ensuring the confidentiality of the Safety and Acknowledgement Message.
- successful transmission and receipt of encrypted and digitally signed Safety and Acknowledgement Messages

Source: EU ICSR Implementation Guide, July 2017

Regional Implementation Guides

Electronic Gateway

A **gateway** is a link between two computer **programs** or systems such as Internet Forums. A **gateway** acts as a portal between two **programs** allowing them to share information by communicating using protocols on a computer or between dissimilar computers1

A gateway uses a combination of public/private key encryption to secure transmission of safety messages

The regional IG should:

- specify the process for establishing a trading partner relationship and specify the types of encryption keys required (for example, self-signed or managed)
- Fully describe the testing procedure for establishing a gateway connection
- Fully describe the testing protocol for verifying submitted messages meet business requirements
- specify the hours of support for technology related issues.
- Specify the supported protocols (web (AS2), email (AS1), etc)

[1]https://en.wikipedia.org/wiki/Gateway_(computer_program)

Source: EU ICSR Implementation Guide, July 2017

Regional Implementation Guides

Additional methods of electronic submission

In addition to electronic gateway, some regions provide additional methods for submitting safety messages

- Web Trader
  - an alternative solution to the use of a local Gateway to support the electronic transmission of Safety and Acknowledgement messages.
  - Allows registered EDI Partners to exchange EDI Messages

- Web Based Portal
  - allows registered EDI Partners to generate fully ICH E2B(R3) compliant Safety and Acknowledgement Messages and to electronically upload these messages securely
  - May allow registered EDI partners to view the date of the transmission of all EDI Messages that have been sent and received.

Source: EU ICSR Implementation Guide, July 2017

Regional Implementation Guides

Business Continuity

System failures may occur at either the send or receiver side

Examples include

- Failure to generate safety messages
- Transmission failure by sender gateway
- Failure of message receipt
- Processing failure at recipients database

The regional IG should specify the procedures to be followed in each failure scenario

Source: EU ICSR Implementation Guide, July 2017

Regional Implementation Guides

Region Specific Business Rules

The Regional IG should contain technical details for composing a valid ICSR. Details should include:

- Information required by the message header such as XML character set information
- Location of XML schemas used to validate safety messages
- Valid values for specific fields such as message type and any region specific allowable values
- Information on receiver identifiers used for gateway routing or internal message routing
- Information on how to submit attachments and the allowable file formats, media types, representation, or compression
- Information on the use of local language in safety messages
- Specific guidance on regional requirements for specific data elements – if applicable
- Information on data elements that are mandatory for a particular region
- Guidance on regional business rules – see document "11_ICH E2B(R3) Core Data Elements and Business Rules ver.1.00.xlsx" in the ICH
  Complete package for format

Source: EU ICSR Implementation Guide, July 2017

Considerations for E2B implementation

Joint planning and collaboration help ensure successful transition

Draft Regional Implementation Guideline and circulate for public comment

Provide regular updates on progress

Conduct public meetings with stakeholders to

- Enable two-way communication for questions and status
- Collect feedback from implementors
- Resolve challenges and answer questions

Conduct Regional Pilot to validate plans and assumptions

Source: EU ICSR Implementation Guide, July 2017

Differences between E2B(R2) and E2B(R3)

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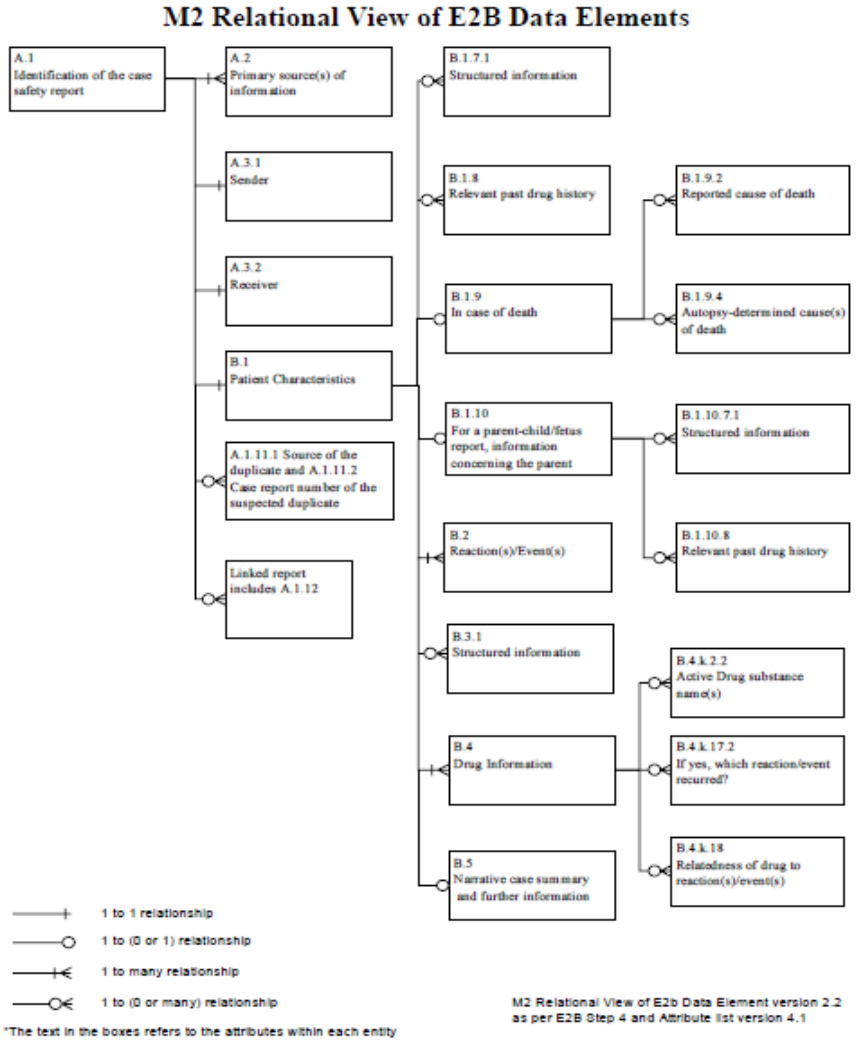
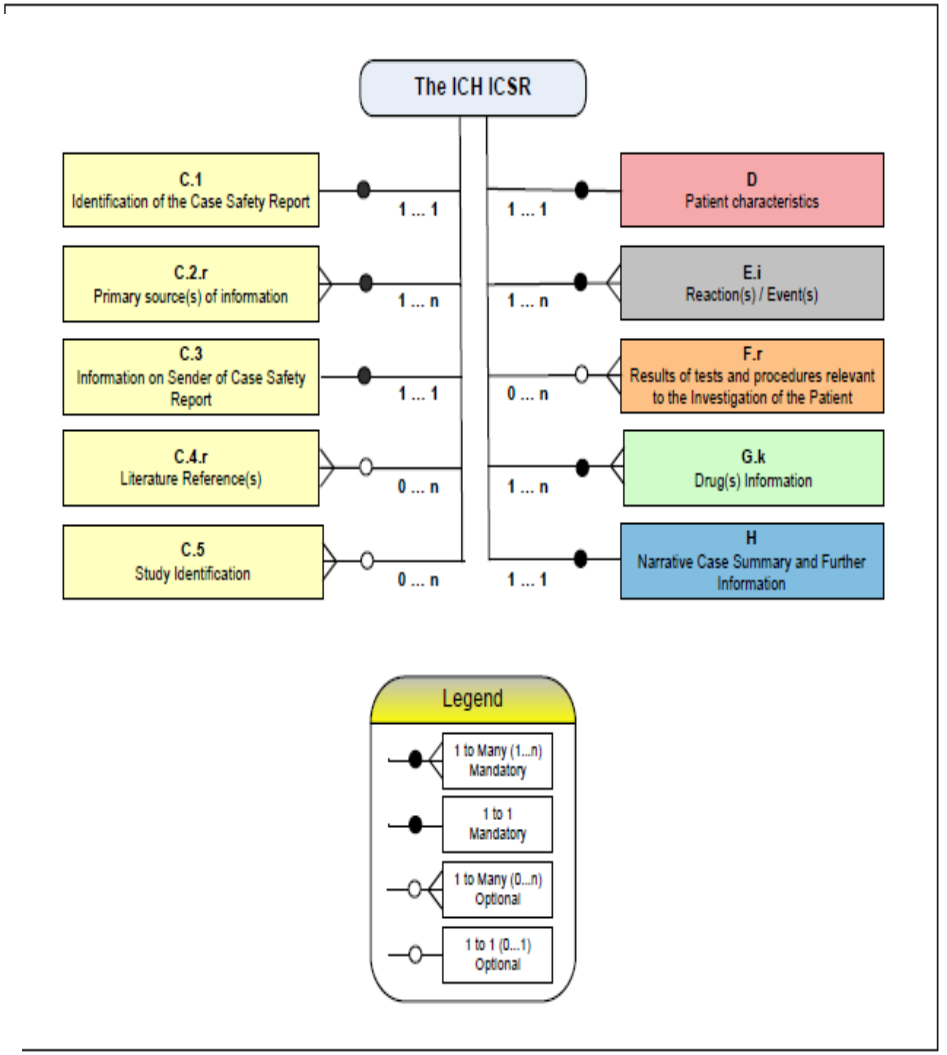
E2B(R2) comparison with E2B(R3)





Changes/Differences E2B(R2) and (R3)

Differences between versions

Concept	R2	R3
Amendment Reports	N/A	Reports may be nullified or amended
Attachments	Provided separately from the message	Embedded in the ICSR
Seriousness Criteria	Case Level	Event Level
Medical Confirmation	Case Level	Event Level
Country of Occurrence	Case Level	Event Level
Null Flavors	N/A	Used to indicate why information may be missing
IDMP – Identification of Medicinal Products	N/A	Ability to use controlled vocabularies when available

Additional Key Differences

New, Changed and Expanded Data Elements

Section C.1 – Identification of the Case Safety Report

ID	Description	Change
C.1.6.1.r.1	Documents Held by Sender	Expanded from 100 to 2000 characters
C.1.9.1.r.1	Source(s) of the Case Identifier	Expanded from 50 to 100 characters
C.1.11.2	Reason for Nullification / Amendment	Expanded from 200 to 2000 characters

Amendments are new in E2B(R3). E2B(R2) only allowed Nullification

Additional Key Differences

New, Changed and Expanded Data Elements

Section C.5 – Study Identification

ID	Description	Change
C.5.2	Study Name	Expanded from 100 to 2000 characters
C.5.3	Sponsor Study Number	Expanded from 35 to 50 characters

Section E.i – REACTION(S)/EVENT(S) (REPEAT AS NECESSARY)

ID	Description	Change
E.i.1.1a	Reaction / Event as Reported by the Primary Source in Native Language	Expanded from 200 to 250 characters
E.i.1.2	Reaction / Event as Reported by the Primary Source for Translation	New in E2B(R3)

Additional Key Differences

New, Changed and Expanded Data Elements

Section G.k DRUG(S) INFORMATION (REPEAT AS NECESSARY)

ID	Description	Change
G.k.2.2	Medicinal Product Name as Reported by the Primary Source	Expanded from 70 to 250 characters
G.k.2.3.r.1	Substance / Specified Substance Name	Expanded from 100 to 250 characters
G.k.7.r	Indication for Use in Case (repeat as necessary)	More than one indication can be provided
G.k.11	Additional Information on Drug (free text)	Expanded from 100 to 2000 characters

Additional Key Differences

New, Changed and Expanded Data Elements

Section H – NARRATIVE CASE SUMMARY AND FURTHER INFORMATION

ID	Description	Change
H.2	Reporter's Comments	Expanded from 500 to 20000 characters
H.4	Sender's Comments	Expanded from 2000 to 20000 characters
H.5.r.1a	Case Summary and Reporter's Comments Text	New field in E2B(R3) for local language requirements

Transitioning from R2 to R3

Some considerations

- The transition from E2B to E2B(R3) will take time
- Global companies will need to be prepared to exchange messages using both E2B(R2) and E2B(R3)
- The backwards/forward compatibility (BFC) document provided by ICH in the E2B(R3) IG provides a starting point for analyzing incompatibilities
- Conversion tools are available for use with major commercial safety database products

Transitioning from R2 to R3

A General Approach for Analysis

1. Review each E2B(R3) data element section by section
2. Map each E2B(R2) and E2B(R3) Data Element to fields in your safety database. Identify any gaps.
3. Decide how to handle E2B(R3) data elements that do not currently exist in your safety dataset. Do you need to add any new fields? Are any conversions required? Have you defined all the necessary business rules?
4. Identify data changes that may impact business processing. For example, does your database support seriousness at the event level?

Thank you

Questions?

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Refrences

Reference sources for this presentation

ICH Efficacy Guidelines:

- https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

Electronic Standards for the Transfer of Regulatory Information (ESTRI) Web-site:

- Message Specification and Q&A for E2B(R2)
- E2B(R3) Implementation Guide and Q&A
- http://estri.ich.org/index.html

M2 Information Paper for OIDs and UUIDs:

- http://estri.ich.org/recommendations/OID_Information_Paper.pdf

Information on use of EDQM terminologies for Dosage Forms and Routes of Admin

- http://estri.ich.org/e2br3/E2B-R3_ExplanatoryMemorandumEDQM_SignOff_2018_0306.pdf

Eudravigilance Website

- https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

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