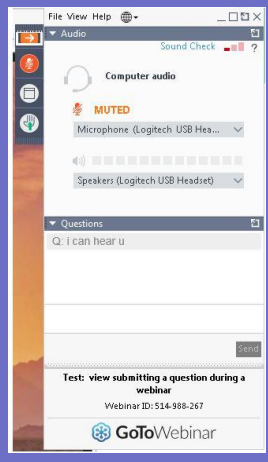
Welcome to the European MedDRA Users Group Webinar on
'Quality of MedDRA Coding'

The session will be chaired by Anne Gyllensvärd
Liz Thomas from the MSSO will provide technical support



Asking Questions

Submitting questions during the presentation:

- Pop out the control panel located in the upper right of your screen
- Type your question into the question box
- When finished typing your question click the 'Send' button
- Questions will be addressed at the end of the webinar.
- Due to time constraints, we may not be able to answer all questions submitted.

Frequently Asked Questions

- Will I be able to get a copy of these slides?

YES

- Is this Webinar being recorded so that I or others can view it at a later time?

YES

Welcome from the European Industry MedDRA Users Group Steering Committee


Morell David


Anne Gyllensvärd


Barry Hammond


Jane Knight


Claudia Lehmann


Claudia Luenzmann


Felix Mader


Martin Menke


Ian Slack


Christina Winter

Agenda

- The PtC Companion Document – Guidance on Quality
  Christina Winter, GSK
- Coding Quality – Regulator's Perspective
  Sonja Brajovic, FDA
- Coding Quality – Company's Perspective
  Ian Slack, Vertex
  Martin Menke, CSL Behring
- Q&A

The PtC Companion Document – Guidance on Quality

Christina Winter, GSK

Coding Quality – Regulator's Perspective

Sonja Brajovic, FDA

Coding Quality – Company's Perspective

Ian Slack, Vertex
Martin Menke, CSL Behring

Q&A Session


THANKS

European MedDRA Users Group Webinar

23 Oct 2018

MedDRA Points to Consider

Companion Document

(Section 2: Data Quality)

Christina Winter
GlaxoSmithKline

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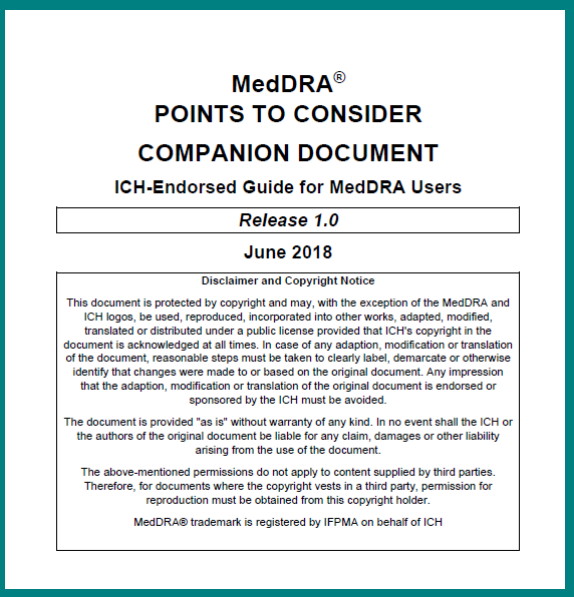

MedDRA®
POINTS TO CONSIDER
COMPANION DOCUMENT
ICH-Endorsed Guide for MedDRA Users

Release 1.0

June 2018

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Companion document*

Release 1.0
(June 2018)

1. Introduction
2. Data Quality
3. Medication errors (not in this presentation)

*'Support information' page, MSSO website

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Introduction

- Supplements Points to Consider Term Selection and Data Retrieval documents
- Produced by same group as documents above
- 'Living' document: updated as needed (not tied to MedDRA versions)
- In English and Japanese
- Content agreed by all ICH parties
- Does not address regulatory requirements or database issues

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Data quality

- MedDRA coded data used for
  - Clinical development
  - Product labelling
  - Safety signal detection, etc.
- Verbatim coded manually, autoencoders
  - Small differences can result in significant issues and misleading analyses
  - Important to thoughtfully evaluate AE data

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Clinical trials

- Collecting high quality data saves resource
  - Less querying – time and cost efficiency
  - Decrease clinical site monitoring costs
  - Reduce risk of delay in regulatory approval
- Consider
  - Training site study staff (especially investigators)
  - Appropriate data collection tools (CRFs)

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Clinical trials

- Trials/projects can run over years
  - Need subject matter experts for data collection tools: data management, statistics, information technology, quality assurance, regulatory compliance
  - After years, not possible to compensate for earlier inadequate data collection
- Data queries
  - Using appropriate techniques (non-directed questioning)
  - Despatched as soon as possible

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Vague reports require clarification

- Had MI
  - Mitral insufficiency?
  - Myocardial infarction?
  - Mesenteric ischaemia?
- Nitro drip
  - Nitroprusside drip?
  - Nitroglycerin drip?

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MedDRA coding considerations
Clinical and post marketing

- Train coders and data reviewers
- Awareness of regulatory considerations for quality data collection
- Follow principles in Points to Consider Term Selection (PtC TS)
- If not using preferred option in PtC TS, document organisation's choice for consistency
- Synonym lists help consistency

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MedDRA coding considerations 2
Clinical and post marketing

- Quality assurance checks / Metrics
- Before database lock / periodic checks of post marketing coding

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Helpful tips

- Unqualified Test Name List
  - Test names intended for database field (e.g. *Blood* glucose)
  - Not for Adverse Events (AEs)
- MedDRA versioning strategy
  - Best practice document ('Recommendations for MedDRA implementation and versioning for clinical trials' and 'Recommendations for single case reporting using semi-annual version control')

Both are on 'Support documentation' page of MSSO website

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Personal example 1

(Not in Companion document)

Verbatim

- Colonies of urine bacterials increased
- Urine bacterials positive
- Urine bacteria increased

Coded term (n)

- *Bacterial test* (5)
- *Bacterial test positive* (1)
- *Bacterial test positive* (1)

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Personal example (1 continued)

- In AE tables of draft clinical study report
  - Post datalock: Too late for data query/recoding
  - Solution: Mark AEs in table and use footnotes to link AEs
- What went wrong?
  - Central data management very familiar with MedDRA
  - This was a local/single country study – to facilitate change in manufacturing site
- Lesson learnt: Don't be complacent!

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Personal example 2
(not in companion document)

- Verbatim = Important urine emissions
- Coded term = *Urine abnormality*
- Context
  - Spontaneous report: patient receiving anti-epileptic drug with insufficient seizure control. Still has seizures and 'important urine emissions'.
  - Translation from non-English speaking country, where MedDRA is relatively unfamiliar

  No possibility of data query as reporter is not contactable. Is this urinary incontinence?

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Questions - at end of webinar

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MedDRA Coding Quality – Focus on Medication Errors

Sonja Brajovic
Medical Officer
FDA/CDER/Office of Surveillance and Epidemiology

Disclaimer

- The information within this presentation represents the views of the presenter, not necessarily those of the FDA or any other referenced organization
- Medical Dictionary for Regulatory Activities (MedDRA®) is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

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Acknowledgment

Content and slides developed in collaboration with the FDA CDER Division of Medication Error Prevention and Analysis (DMEPA)

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Outline

- ✓Medication error reports in FAERS*
- ✓Quality data
  - Data intake/what to report
  - Coding accuracy
- ✓Tool for coding quality
  - New “MedDRA Points to Consider Companion Document”
- ✓Medication error pharmacovigilance case examples

*FDA Adverse Event Reporting System

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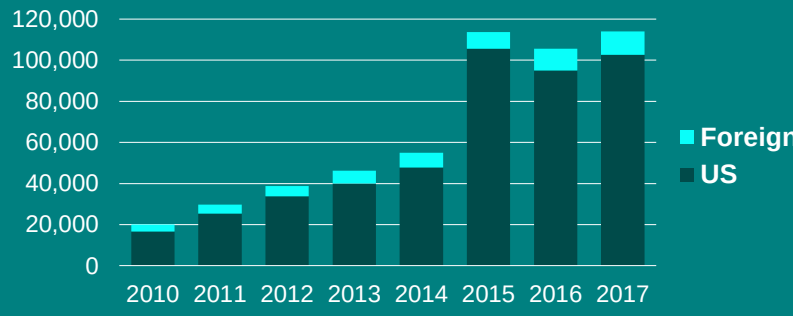
Medication Error Reports in FAERS*



*Based on the MedDRA SMQ *Medication errors (narrow)*, V21

5

Challenges With Medication Error Pharmacovigilance

- ✓ Different medication error terminology, reporting requirements, labeling and product design, and clinical practices
- ✓ Incomplete reports/lack of reporting forms tailored to capture medication error information
- ✓ Accurate product identification
  - Nomenclature (e.g., acetaminophen vs paracetamol, biosimilar suffixes)
  - Products with the same proprietary name but different ingredients
- ✓ Inconsistent and ambiguous coding of medication errors
- ✓ Identifying and reviewing labeling from other countries
- ✓ Timely sharing of information

6

Data Intake/What to Report for Product Use/ Medication Errors

- Describe the sequence of events leading up to the error in sufficient detail so that the circumstances surrounding the error can be understood.

7

For Medication Errors, include

- A description of what happened that led to the error or the circumstances that could cause or lead to an error
- The type of error (e.g., wrong drug or device, improper dose, wrong technique in product use) – NCC MERP terms are now all in MedDRA
- The stage where the error occurred (e.g., prescribing, selection, preparation, dispensing, administration or use, monitoring)
- The causes and contributing factors for the error (e.g., confusing or inadequate labeling, packaging, or instructions for use; look-alike or sound-alike product names)

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For Medication Errors, include (2)

- The setting where the error occurred (e.g., clinic, hospital operating room, home)
- The role of the persons involved in the error (e.g., pharmacist, physician, nurse)
- Recommendations or actions taken to prevent the error from happening or recurring
- Adverse events and outcomes associated with the error (medication errors may or may not result in an adverse event)

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For Medical Device Use Errors

- These errors can arise due to problems with the design of the medical device or the manner in which the device is used.
- Please report device use errors regardless of patient involvement or outcome. Also report circumstances of use or device interactions that could cause or lead to use errors
- Include a description of the device use error, the type of staff involved, the work environment in which the error occurred, and the circumstances or events that led to or contributed to the use errors.

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For Medical Device Use Errors (2)

Medical device use errors can occur for reasons that include the following:

- Device use is inconsistent with the user's expectations or intuition
- Device use requires physical, perceptual, or cognitive abilities that exceed those of the user
- Devices are used in ways that were not anticipated by the manufacturer
- The device's labeling or packaging is confusing or inadequate
- The environment adversely affects or influences device use

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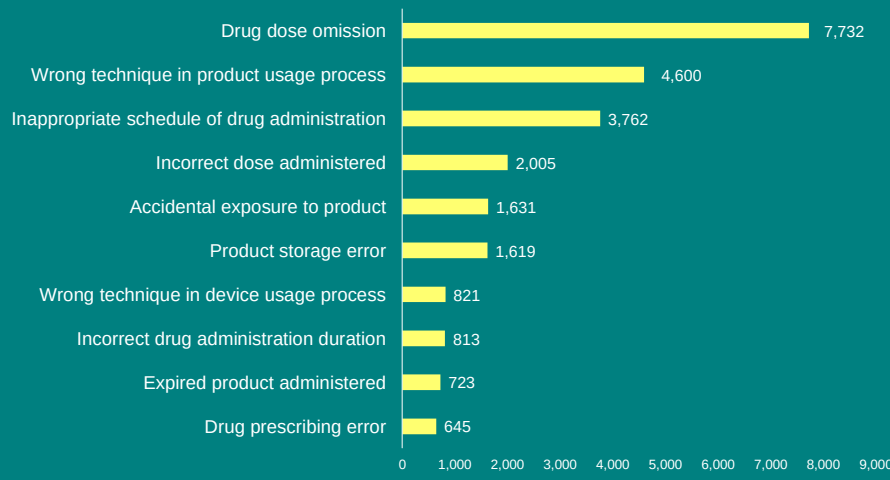
Top 10 Reported U.S. Medication Error PTs* 01Jul2018-30Sep2018



*Based on the MedDRA SMQ *Medication errors (narrow)*, V21

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Top Reported PTs from SMQ *Medication Errors* broad scope 01Jul2018-30Sep2018, US cases

Top reported PTs for SMQ Medication errors (broad)	Case Count	Percent
Drug dose omission	7,732	20.8%
Wrong technique in product usage process	4,600	12.4%
Product use in unapproved indication	4,115	11.1%
Inappropriate schedule of drug administration	3,763	10.1%
Product use issue	2,115	5.7%
Underdose	2,106	5.7%
Incorrect dose administered	2,005	5.4%
Overdose	1,820	4.9%
Accidental exposure to product	1,632	4.4%
Product storage error	1,619	4.4%
Device malfunction	952	2.6%
Wrong technique in device usage process	822	2.2%
Incorrect drug administration duration	812	2.2%
Product adhesion issue	770	2.1%
Expired product administered	723	1.9%

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Breakout of Top 3 Reported MedDRA Medication Error PTs by top LLTs

PT *Drug dose omission* (n=7,732)		**PT *Wrong technique in product usage process* (n=4,600)**		**PT *Inappropriate schedule of drug administration* (n=3,763)**	
LLT	**Case Count**	**LLT**	**Case Count**	**LLT**	**Case Count**
Missed dose	6,715	**Wrong technique in product usage process**	**2,171**	**Inappropriate schedule of drug administration**	**2,053**
Drug dose omission	**982**	Wrong technique in drug usage process	1,423	Once daily dose taken more frequently	948
Missed dose in error	38	Product cleaning error by user	361	Drug dose administration interval too long	280

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Overview of LLT-PT Use

FAERS Data Request FDA Receive Dates 01Jul2018 – 30Sep2018	# of cases	Comment
Number of US FAERS cases coded with a PT from the SMQ *Medication errors (narrow)*	27,359	SMQ *Medication errors (broad):* 37,103 US cases
Number of US FAERS cases coded with a single PT from the SMQ *Medication errors (narrow)*	27,301	
Number of US FAERS cases where the medication error PT in the SMQ *Medication errors (narrow)* equals the LLT	13,038 (48%)	~Half of cases are coded with LLT=PT; there is a need to increase the use of specific LLTs in coding

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MedDRA PtC Companion document

Framework towards harmonization of terminology and coding

"The purpose of this Companion Document is to supplement the Points to Consider (PtC) documents by providing additional details, examples, and guidance on specific MedDRA-related topics of global regulatory importance."

"The Companion Document is intended to be a "living" document and is updated based on users' needs".

Table of Contents:

- Introduction
- Data Quality
- Medication errors

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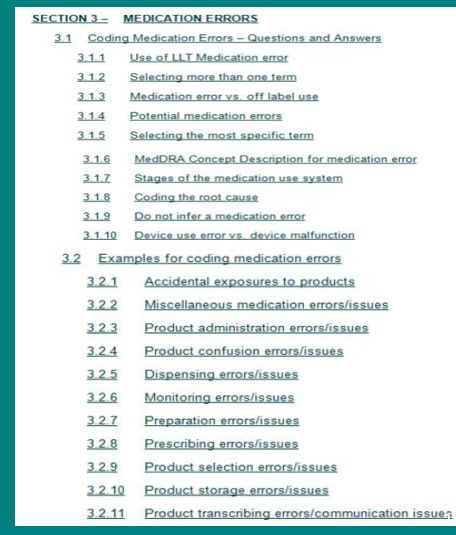
MedDRA PtC Companion document

Table of Contents



From the Companion Document (1)

- **Product administration errors/issues**
  - **Dose omission**

- "As per the MedDRA Concept Description, dose omission is 'the failure to administer an ordered dose to a patient before the next scheduled dose, if any. This excludes patients who refuse to take a medication, a clinical decision (e.g., contraindication), or other reasons not to administer (e.g., patient sent for test).
- For the purposes of retrieval and analysis, in general, a dose omission should be considered to be a suspected medication error. There may be scenarios where doses are missed which are not considered medication errors and therefore a term such as LLT *Therapy interrupted* should be used to help to distinguish these. LLT *Therapy interrupted* / PT *Therapy cessation* is included in HLT *Therapeutic procedures NEC* and is not a medication error concept."

From the Companion Document (2)

- **Product administration errors/issues**
  - **Dose omission**

Scenario	Medication error?	LLT	Comment
Health provider was unable to mix the contents of the two syringes because the plunger was stuck, and this resulted in leakage where the two syringes were connected. The defective plunger resulted in the dose not being given.	Yes	Drug dose omission Syringe issue	This is an example of a product quality issue leading to a medication error
Scenario	**Medication error?**	**LLT**	**Comment**
Patient took the drug as prescribed but broke out in a red itchy rash and did not take the remaining doses	No	Itchy rash Therapy cessation by patient	Stopping therapy because of an adverse event does not represent an error or intentional misuse
Patient habitually skipped prescribed antipsychotic	No	Treatment noncompliance	

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MedDRA LLT Specificity Example

- PT *Wrong technique in product usage process* v21.1

PT Wrong technique in product usage process
- LLT Inappropriate chewing of medication
- LLT Inappropriate cutting of medicated plaster
- LLT Inappropriate cutting of transdermal delivery system
- LLT Inappropriate cutting of transdermal patch
- LLT Inappropriate drug extraction with syringe
- LLT Inappropriate removal of drug from capsule
- LLT Incorrect needle gauge used
- LLT Inhalation not administered correctly
- LLT Needle priming not performed
- LLT Product cleaning error by user
- LLT Tablet crushed incorrectly
- LLT Tablet split by mistake
- LLT Tablet split incorrectly
- LLT Unapproved crushing of product
- LLT Unapproved splitting of product
- LLT Wrong injection technique
- LLT Wrong technique by user in product cleaning
- LLT Wrong technique in drug usage process
- LLT Wrong technique in product usage process

How to increase specificity in coding:

- - add more specific LLTs?
- split an existing PT into two or more PTs with their specific LLTs?
- both approaches, depending on LLTs and their PT?

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From the Companion Document (3)

- **Selecting the most specific term**

- **"How should terms that have overlapping concepts with other terms be used?**
- For example, a report described a patient who did not allow a product adequate time to reconstitute before self-administering.
- The most specific available LLT should be selected for the reported information. For the above example, select LLT *Inappropriate reconstitution technique* (PT *Product preparation error*) because it is more specific than LLT *Wrong technique in product usage process (PT Wrong technique in product usage process)*. Coding a singular error by selecting two error terms is useful only when this provides meaningful additional information, i.e. when the single LLT cannot describe the entire reported scenario."

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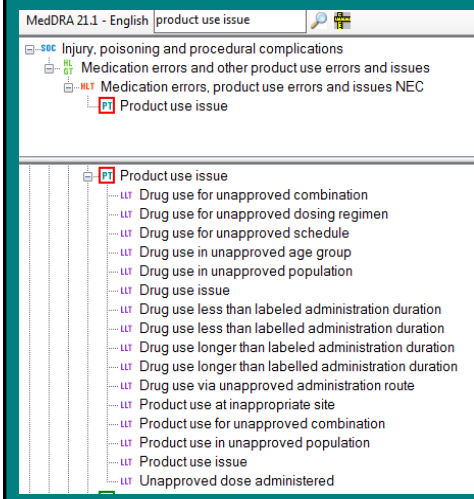
MedDRA LLT Specificity example (2)



- MedDRA v21.1 collapses many 'unapproved use scenarios' under a single PT *Product use issue*
- Coding at this PT level is of very limited value; only the specific LLT conveys relevant information

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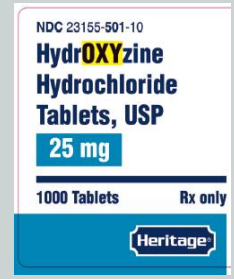
Pharmacovigilance Case Example: Look Alike Container Labels

In 2016: spike in reports about look alike container labels for HydrALAZINE and HydrOXYzine

BEFORE	AFTER



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Pharmacovigilance Case Example: Product Name Confusion

FDA received reports describing confusion between two proprietary names, Depo-Medrol and Depo-Provera, and their respective established names, methylprednisolone and medroxyprogesterone

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Pharmacovigilance Case Example: Product Name Confusion

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	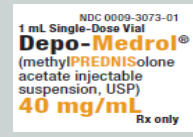
	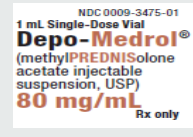
	

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(Finally….)

Thank you!

Questions - at end of webinar…

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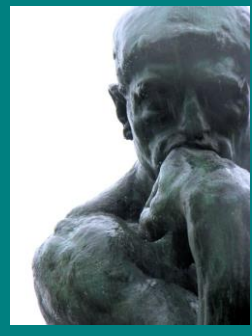
European MedDRA Users Group Webinar

Industry Perspective on MedDRA Coding Data Quality

Ian Slack & Martin Menke | 23rd October 2018

What should we consider when thinking about Data Quality?

- Source Data Quality
- Coding Resources & Training
- Coding Review & Oversight
- Metrics



Source Data Quality – Clinical Trials

Rubbish In = Rubbish Out

(For our American colleagues…. Trash In = Trash Out)

Why do we get Rubbish at source?

- Poor Instructions?
  - Protocol
  - eCRF Completion Guidelines
  - Training
- Resources?
  - 'Clinical Trial naïve' sites – do not understand requirements of a trial well enough
  - 'Experienced' sites – know 'too much' We've always done it this way etc.

Source Data Quality – Post Marketing

Rubbish In = Rubbish Out

Why do we get Rubbish at Source?

- Untrained Reporter who is so aware of the Context that he doesn't tell
- Miscommunication between Reporter and Contact Personnel
- Contact Personnel not clarifying Context
- Translation Issues (e.g. Colloquial Language used by Reporter)

> Resulting in ambiguous or modified Information

- Unmediated Reports without Possibility to follow - up

Coding Resources & Training

Safety Database

Key to have a clear data extraction guideline to identify and enter the right information for coding from the reported narrative.

Clinical Database

Key to have the sites trained effectively to enter the right information into the database for coding purposes.

The eCRF Completion Guideline should contain clear instructions for the site entry staff. These are typically standard instructions but may be different for certain studies or therapeutic areas based on the details needed for collection.

Training should concentrate on the areas of interest regarding detail of data required but should not ignore the basic principles.

Coding Review & Oversight

- Safety Data and Post Marketing
- Sponsor Clinical Data In-House Coding
- CRO Clinical Data Coding
  - CRO uses own system and coding conventions
  - CRO uses own system but sponsor coding conventions
  - CRO has access to sponsor's system and uses sponsor's coding conventions ("ext. in-house coding")
  - CRO is working for multiple sponsors

Coding Review & Oversight – Post Marketing

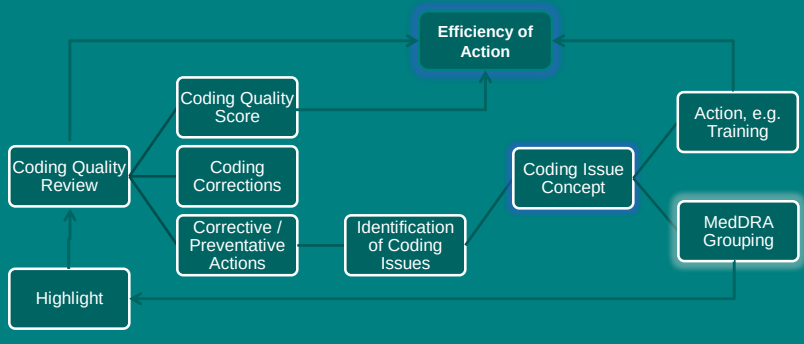
GVP I lists coding as a critical pharmacovigilance process (I.B.11.3.)

Accordingly the Quality Cycle (I.B.3.) needs to be in Place, including :

- Quality Control and Assurance of Coding
  With
- Quality Improvements (CAPAs) when required.

Whoever and wherever the coding is done the MAH needs to maintain oversight and be able to provide proof of this.

Coding Review & Oversight – Process Flow



Metrics

What Metrics do you collect?

Quality of coding is also dependant on quality of process, planning, documentation and training.

Are the collected metrics different based on In-House vs Outsourced coding?

Are metrics used as KPIs?

Is there an escalation process for persistent poor quality?

Example Metrics

Timelines

- Coding Plan (including coding conventions) development and approval (prior to DB go-live)
- Coding tool configuration and testing (prior to First Subject First Dose)
- Frequency Agreement
  - How often should coding be performed?
  - Time from Data Entry to Coding & QC
- Turnaround time for coding reviews for study deliverables

Oversight Metrics

- Periodic Metrics (usually monthly) to ensure the CRO is on top of the study work especially when approaching deliverables.
- Backlog of coding and coding query management can impact quality

Example Metrics

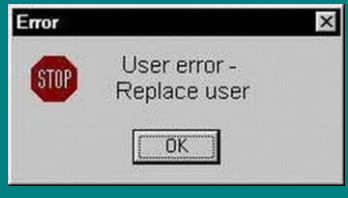
Coding Correctness

- Measurable based on Sponsor or Medical Review vs conventions and defined process (Coding Plan)
- Error rate can be calculated based on ALL Unique Terms coded (Autoencoded terms & Manually coded terms) or could be based on just Interactive / Manually coded Unique Terms
- MedDRA level should be defined when calculating error rates
  - LLT – Most Granular and applicable to conventions / PTC
  - PT – Unique Clinical concept / used for TFLs
- Errors could be defined as:
  - Incorrect coding based on Therapeutic Area or standard conventions
  - Terminology coded that requires a query and a query has not been raised

Example Metrics

Coding Queries

- Important to have quality coding queries
- Standard query text can help
- Coding Query Error could be defined as:
  - Queries raised in error
  - Queries raised with poor query text resulting in re-query
  - Coding was performed but a Query should have been raised



Example Metrics – Post Marketing

Timelines

- Continuous monitoring
- Short Response Time required to avoid pseudo-late Reports due to Coding Corrections (if you can't do E2B-R3, yet).

Oversight Metrics

- Periodic Metrics dependent on Volume and Number or required Corrections.
- Identification of Coding Issues.
- Check of Effectiveness of Corrective Actions

Coding Correctness

- Measurable based on Verbatim to Lowest Level Term Allocation Ratio

Summary slide

Coding data quality considerations

- Define Data Quality
- Understand that Quality starts at source
- Process and Resource impacts
- Differences between Clinical Trials and Post Marketing data
- Set expectations and KPIs
- Collect and monitor Quality Metrics

Thankyou