

Risk based approach on coding quality review in ICTs + differences and considerations in postmarketing



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Coding and data quality

Last European MedDRA User Group webinar focused on Data Quality

- Introduction to PTC Companion document with focus on data quality
- Industry perspective presentation on MedDRA coding data quality

The webinar was recorded and can be accessed on <u>https://www.meddra.org/user-groups</u>

MedDRA[®] POINTS TO CONSIDER

COMPANION DOCUMENT

ICH-Endorsed Guide for MedDRA Users

Release 1.0

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INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE ICH

E6(R2)

ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other

Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice

5. SPONSOR

ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2 Risk Identification





Define safety profile

→1st risk based decision: where to put coding / review efforts?

Show efficacy



Data collected in CRF

- CRF design is important and good design helps generate high quality data
- Training on collection of data equally important

Data documented in database and processed

Coding

• Statistical analysis including imputation methods





Technical measures for consistency / automation:

- Use of synonym lists
- Use of coding conventions
- Standard terms to be queried
- Unique verbatim coding





Can we explain findings better, if we know them early?

Randomized, open-label ICT with 2 treatment arms with different opioid medications:

Fatigue expected to occur, but in previous trials only 7% (light green) and 9.4% (dark green)

Not picked up in data review





Could better coding prevent discussions?

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- Product bought from another company with full clinical package
- New submission planned to include further population of patients
- Discussion on painful application: what do we need to look at?

		Salety Analysis	set
Time point	Statistic	(N=186)	Placebo (N=183)
15 minutes after	n	185	183
patch removal			
-	Mean	- <mark>1.6</mark>	-2.0
	SD	2.49	2.08
	Min	- 9	-10
	Q1	-3.0	-3.0
	Median	-1.0	-2.0
	Q3	0.0	-1.0
	Max	9	4
60 minutes after patch removal	n	185	182
1	Mean	-1.8	-2.2
	SD	2.57	2.07
	Min	- 9	-10
	Q1	-4.0	-4.0
	Median	-2.0	-2.0
	Q3	0.0	-1.0

MedDRA v13.1	Treatment, Number of patients (%)			
System Organ Class		Placebo		
Preferred term	N = 186	N = 183		
Overall	65 (34.9)	23 (12.6)		
Nervous system disorders	28 (15.1)	5 (2.7)		
Burning sensation	26 (14.0)	<mark>4 (2.2)</mark>		
Diabetic neuropathy	1 (0.5)	0		
Dysaesthesia	1 (0.5)	0		
Paraesthesia	0	1 (0.5)		
Musculoskeletal and connective tissue disorders	17 (9.1)	9 (4.9)		
Pain in extremity	17 (9.1)	<mark>8 (4.4)</mark>		
Muscle spasms	0	1 (0.5)		
General disorders and administration site conditions	19 (10.2)	5 (2.7)		
Application site pain	18 (9.7)	4 (2.2)		
Application site reaction	1 (0.5)	0		
Oedema peripheral	0	1 (0.5)		
Skin and subcutaneous tissue disorders	5 (2.7)	3 (1.6)		
Pruritus	1 (0.5)	2 (1.1)		
Erythema	2 (1.1)	0		
Blister	1 (0.5)	0		
Rash	1 (0.5)	0		
Urticaria	0	1 (0.5)		
Eve disorders	1 (0.5)	0		

Table 30Summary of Patients with Drug-Related TEAEs (SAF)

10-Apr-2019

Coders are specialized in coding – Drug safety/Clinical scientists are not!

→Basic assumption:
Data management vendor will do a good job in coding

Meaningful to invest efforts in:

- Drug specifics
- Trial specifics
- Frequently reported terms which will need to be analyzed for the safety profile
- Medical concepts of importance
- See the complete picture



Risk based review of safety data

Prioritization

- Medical concept of the reported AE
 - Designated medical events (DME)
 - Product-specific keep-under-review (KUR)
 - Relevant aspects of the trial and/or product
- Frequency of the event
- Severity of the event
- Causal relationship



Examples

	A	В	С
1			
2			
3	Row Labels	Count of Preferred term	Count of Preferred term2
4	Acute phase reaction	14	10.29%
5		10	7.35%
6	Nausea	10	7.35%
7	Headache	8	5.88%
8	Arthralgia	6	4.41%
9	Myalgia	5	3.68%
10	Pruritus	5	3.68%
11	Nasopharyngitis	4	2.94%
12	Complex regional pain syndrome	4	2.94%
13	Vomiting	4	2.94%
14	Pain in extremity	3	2.21%
15	Back pain	3	2.21%
16	Diarrhoea	3	2.21%
17	Bone pain	3	2.21%
18	Urinary tract infection	3	2.21%
19	Blood calcium decreased	2	1 47%

	А	В	
1			
2			
3	Row Labels 🚽	Count of Low Level	terr
4	·	15	
5	Acute phase reaction	14	
6	ACUTE PHASE REACTION	1	
7	ACUTE PHASE REACTION (GENERALIZED ACHINESS M	1	
8	ACUTE PHASE REACTION (HEADACHE)	1	
9	ACUTE PHASE REACTION BACK ACHE	1	
10	ACUTE PHASE REACTION DIARRHEA	1	
11	ACUTE PHASE REACTION HEADACHE	1	
12	ACUTE PHASE REACTION INTERMITTENT RIGHT EYE PI	1	
13	ACUTE PHASE REACTION MUSCULOSKELETAL PAIN	2	
14	ACUTE PHASE REACTION NAUSEA	3	
15	ACUTE PHASE REACTION RIGHT EYE TWINGE	1	
16	ACUTE PHASE REACTION SHORT INTERMITTENT HEAD	1	
17	🗏 Nausea	10	
18	NAUSEA	10	
19	🗏 Headache	8	
20	HEADACHE	8	
21	🗏 Pruritus	5	
22	PRURITIS	5	
23	Complex regional pain syndrome	4	



How to use MedDRA in this context?

Code lists for DME/KUR and other product specific lists e.g. listed events

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Term Term Text ↑= Primary SOC Level Acute generalised Skin and subcutaneous PT exanthematous pustulosis tissue disorders PT Acute hepatic failure Hepatobiliary disorders Blood and lymphatic granulocytosis system disorders Immune system naphylactic shock disorders Immune system naphylactoid shock disorders Skin and subcutaneous ngiolymphoid hyperplasia ith eosinophilia tissue disorders Blood and lymphatic plasia pure red cell system disorders



- Approach needs thinking no one fits all approach!
- What do I know/don't know? where to focus for gaining knowledge?
- What do I expect to see in the population? Background diseases?
- What is occurring more frequently than expected? Unknown unknowns?
- •What are concepts always suspicious AND relevant?
- Do I have enough information within the CRF or do I need to find out more to characterize a signal? → potentially query



Postmarketing – Quality review of coding

Prioritization needed:

- Case type (e.g. 100% SUSARs, x% SAEs, x% non-serious cases)
- Identification of Index and ,Striking' cases during case processing leading to ICSR review by product responsible
- Cases for certain topic of interest are being reviewed during signaling by product responsible Drug Safety Scientist

→ Implementation of E2B R3 will provide the possibility of easier quality improvements in ICSRs



