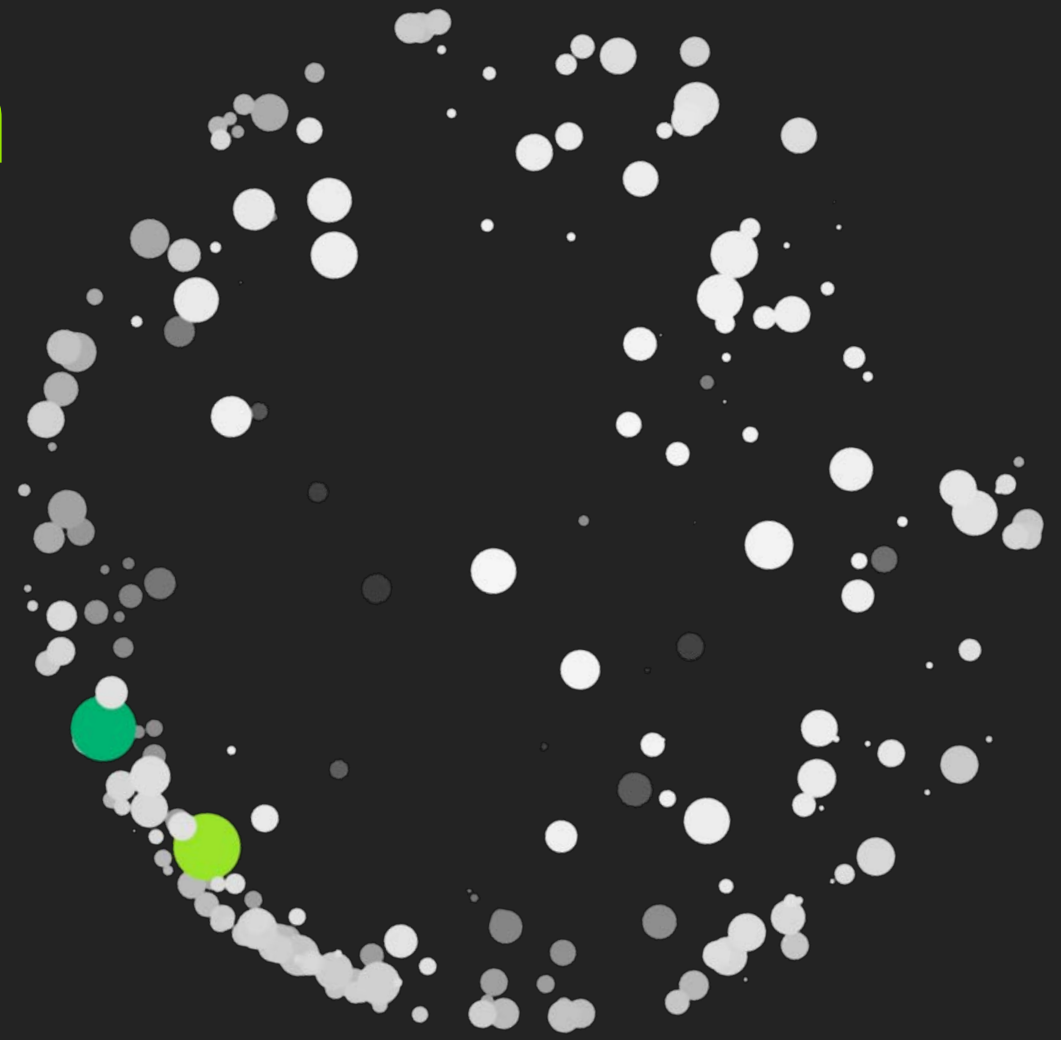
Risk based approach on coding quality review in ICTs + differences and considerations in post-marketing



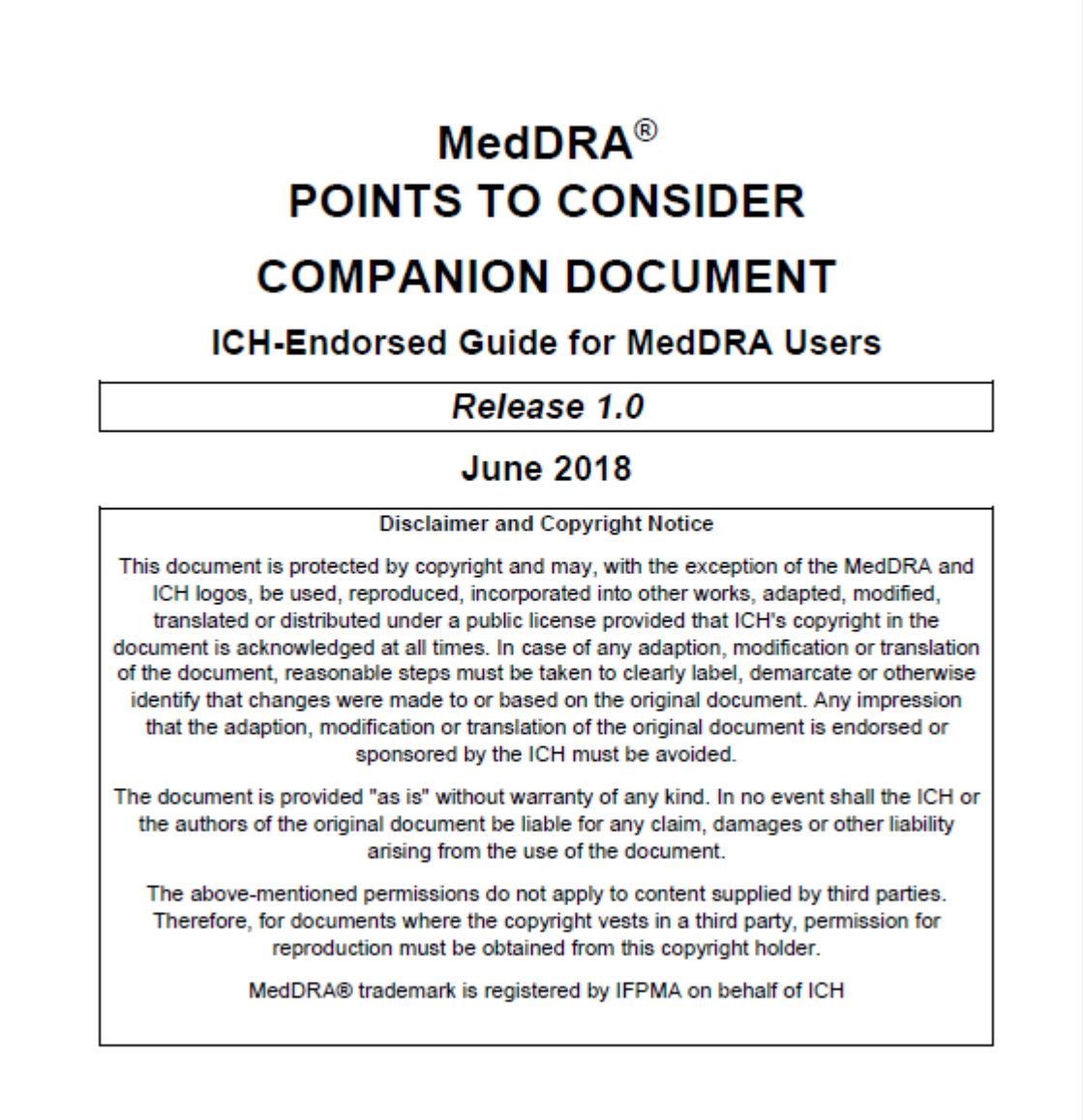
Anne Gyllensvärd

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 https://www.meddra.org/user-groups



MedDRA®
POINTS TO CONSIDER
COMPANION DOCUMENT

ICH-Endorsed Guide for MedDRA Users

Release 1.0

June 2018

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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

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.

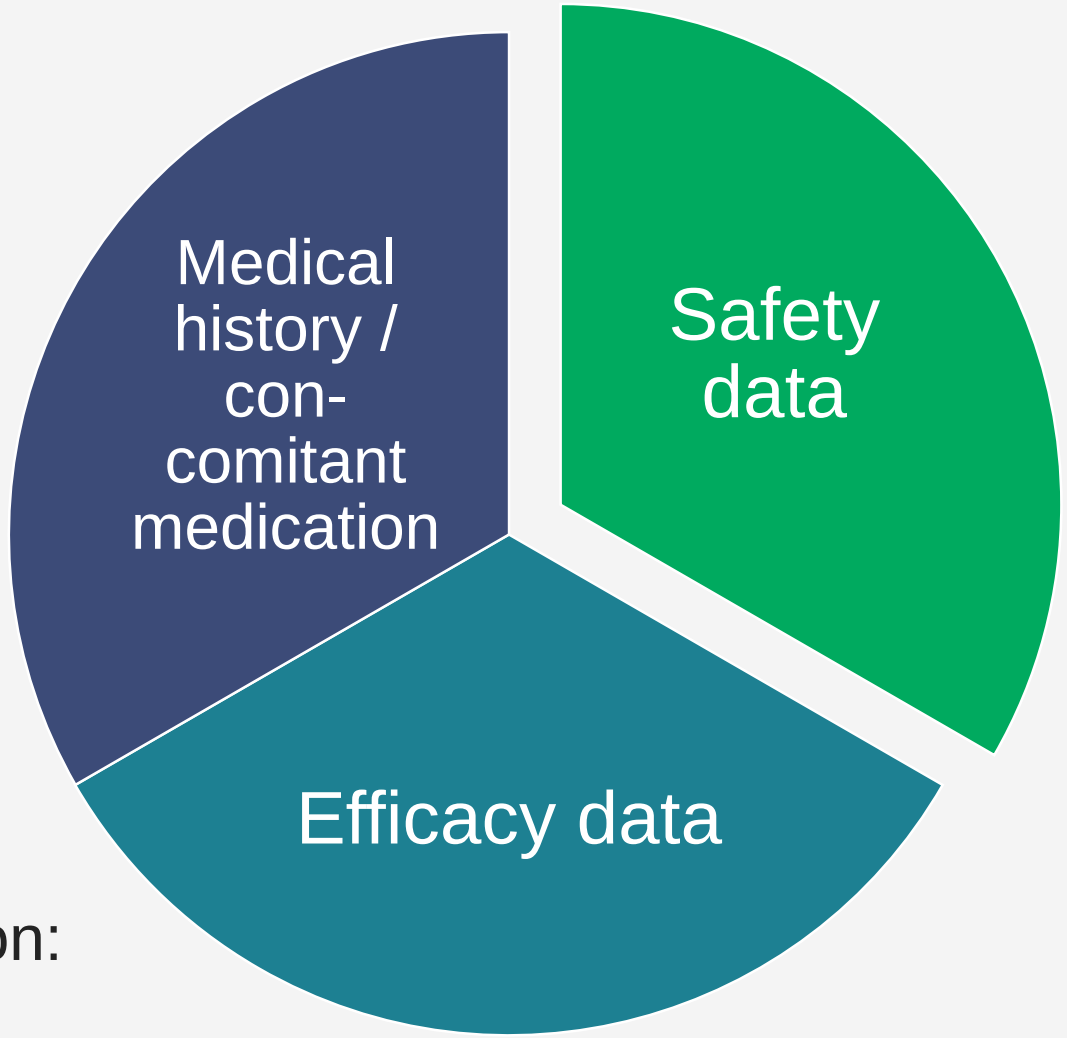
The quality management system should use a risk-based approach as described below.

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 study population



Define safety profile

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

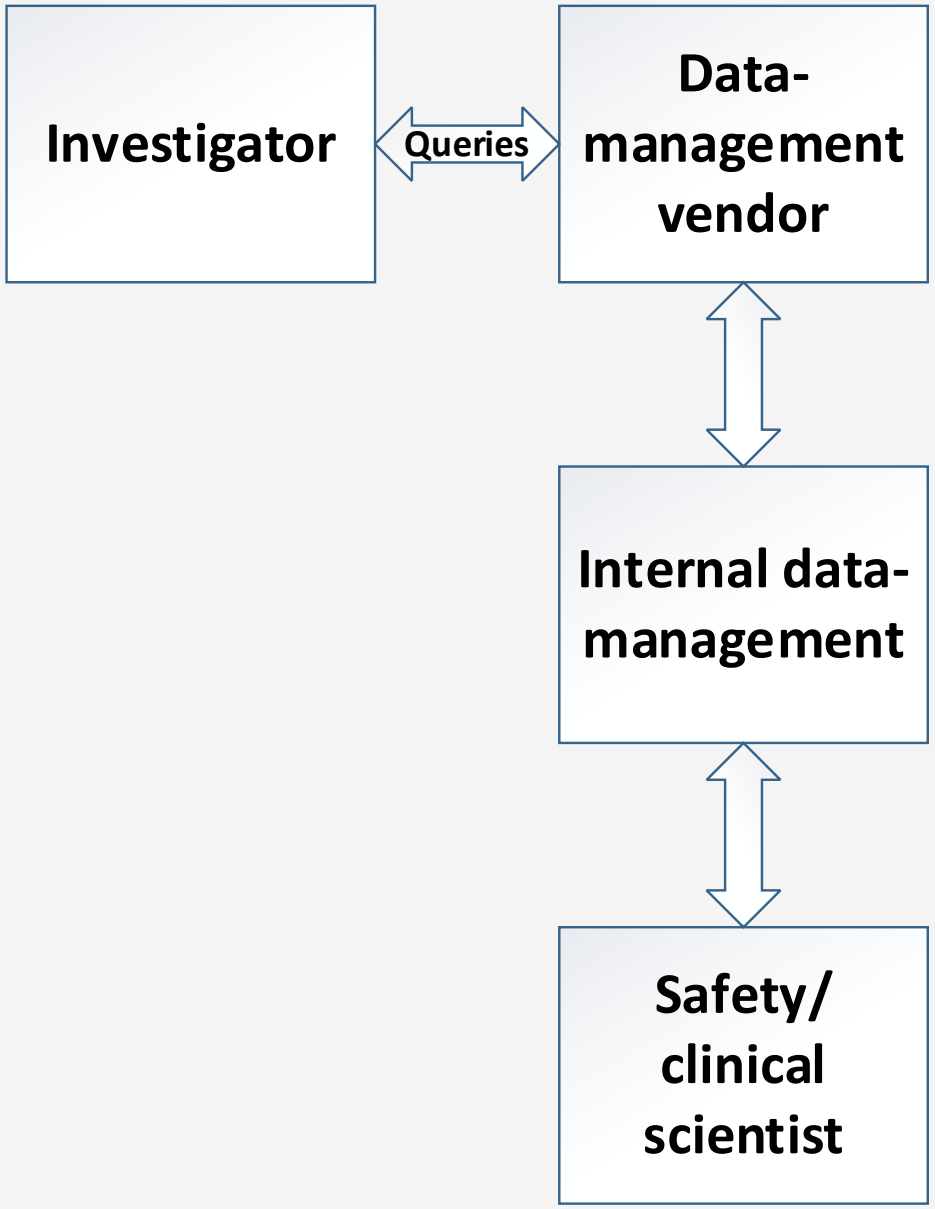
Show efficacy

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



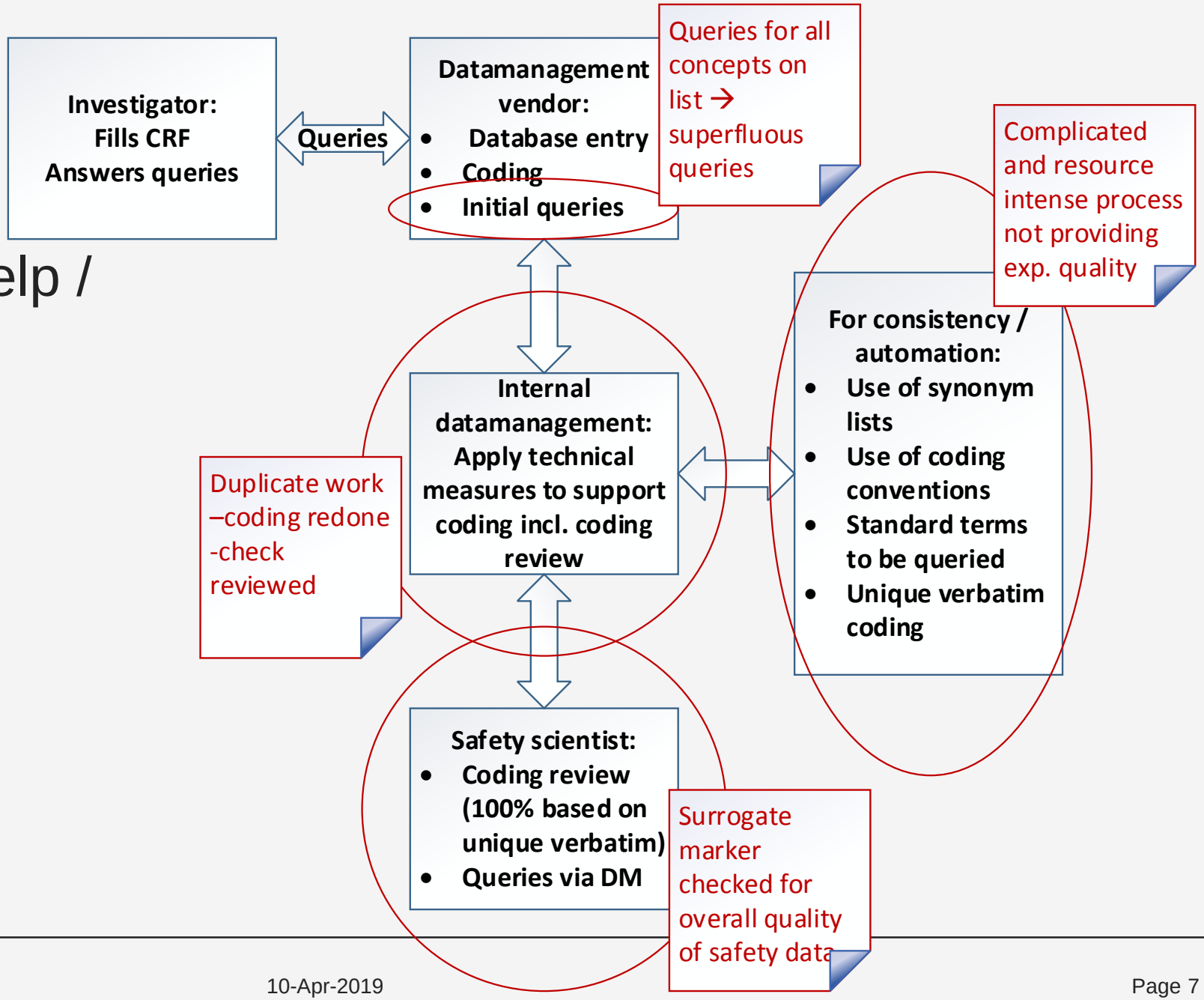
Technical measures for consistency / automation:

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

Where does process help / handicap?

What to focus on?

Who to do what?

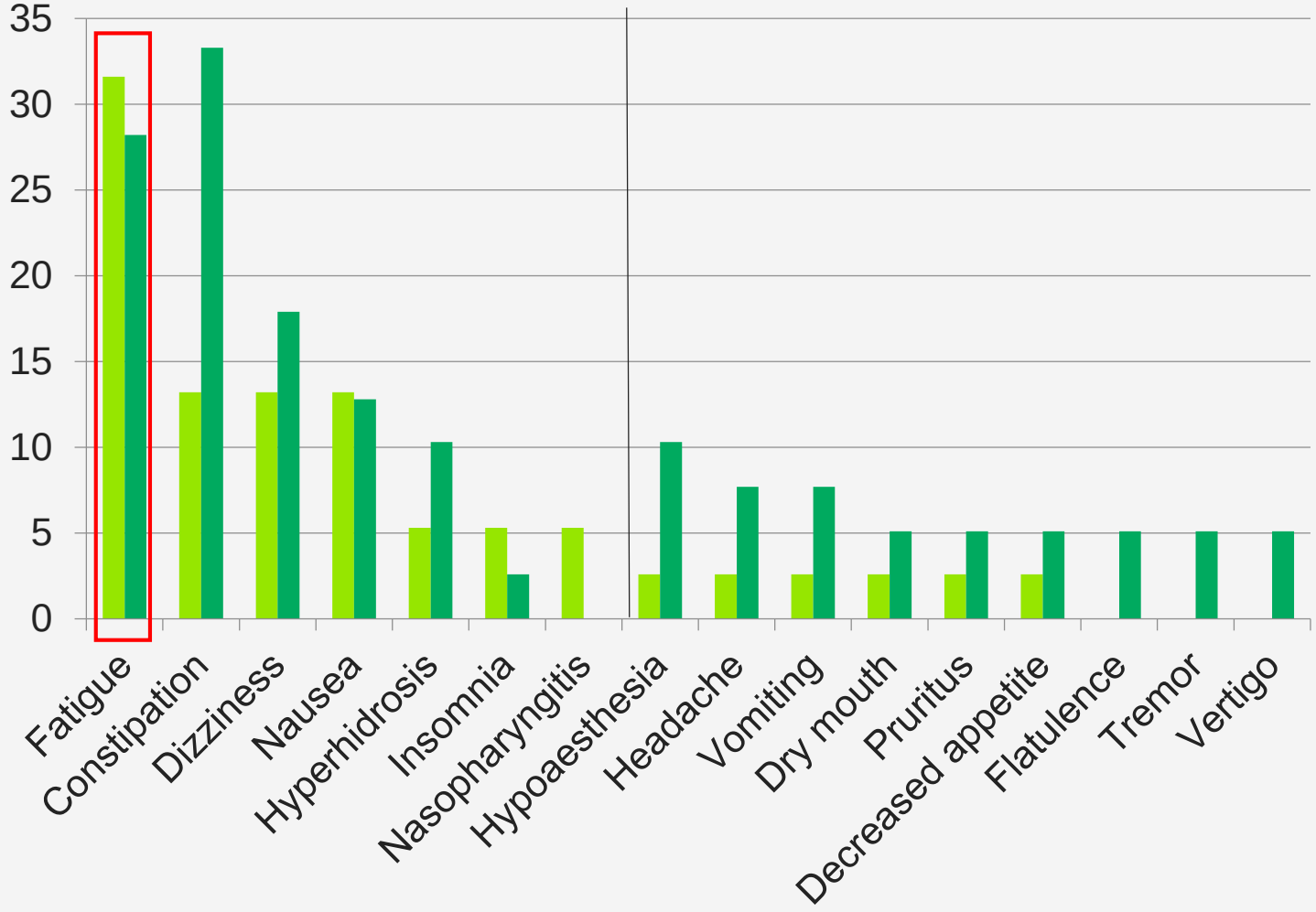


Can we explain findings better, if we know them early?

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?

- 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?

Safety Analysis Set

Time point	Statistic	[redacted] (N=186)	Placebo (N=183)
15 minutes after patch removal	n	185	183
	Mean	-1.6	-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
	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

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

MedDRA v13.1 System Organ Class Preferred term	Treatment, Number of patients (%) [redacted] N = 186	Placebo N = 183
Overall	65 (34.9)	23 (12.6)
Nervous system disorders	28 (15.1)	5 (2.7)
Burning sensation	26 (14.0)	4 (2.2)
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)	8 (4.4)
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)
Eye disorders	1 (0.5)	0

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

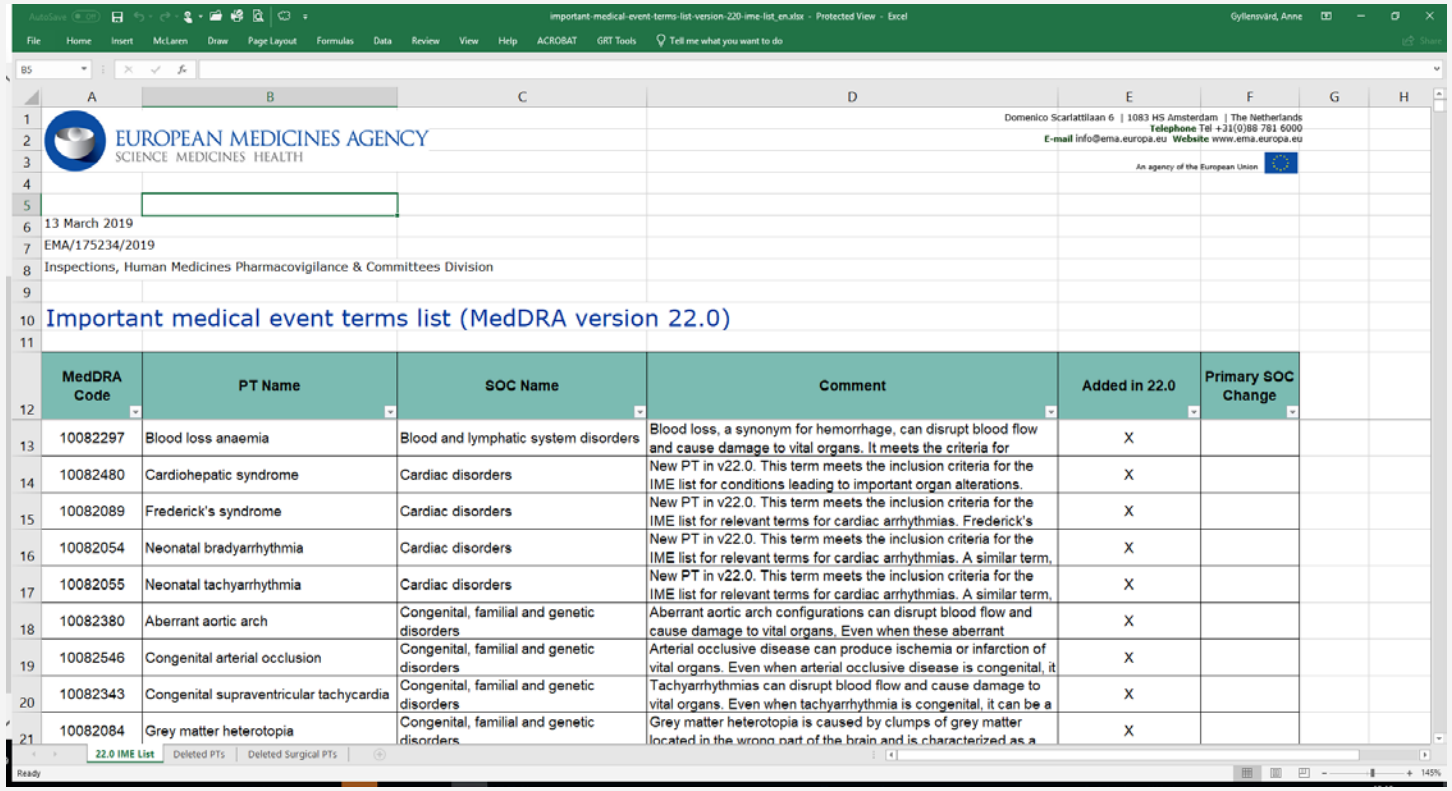
Examples

Row Labels	Count of Preferred term	Count of Preferred term2
Acute phase reaction	14	10.29%
	10	7.35%
Nausea	10	7.35%
Headache	8	5.88%
Arthralgia	6	4.41%
Myalgia	5	3.68%
Pruritus	5	3.68%
Nasopharyngitis	4	2.94%
Complex regional pain syndrome	4	2.94%
Vomiting	4	2.94%
Pain in extremity	3	2.21%
Back pain	3	2.21%
Diarrhoea	3	2.21%
Bone pain	3	2.21%
Urinary tract infection	3	2.21%
Blood calcium decreased	2	1.47%

Row Labels	Count of Low Level terr
⊞	**15**
⊟ **Acute phase reaction**	**14**
ACUTE PHASE REACTION	1
ACUTE PHASE REACTION (GENERALIZED ACHINESS M	1
ACUTE PHASE REACTION (HEADACHE)	1
ACUTE PHASE REACTION BACK ACHE	1
ACUTE PHASE REACTION DIARRHEA	1
ACUTE PHASE REACTION HEADACHE	1
ACUTE PHASE REACTION INTERMITTENT RIGHT EYE PI	1
ACUTE PHASE REACTION MUSCULOSKELETAL PAIN	2
ACUTE PHASE REACTION NAUSEA	3
ACUTE PHASE REACTION RIGHT EYE TWINGE	1
ACUTE PHASE REACTION SHORT INTERMITTENT HEAL	1
⊟ **Nausea**	**10**
NAUSEA	10
⊟ **Headache**	**8**
HEADACHE	8
⊟ **Pruritus**	**5**
PRURITIS	5
⊟ **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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An agency of the European Union

13 March 2019
EMA/175234/2019
Inspections, Human Medicines Pharmacovigilance & Committees Division

Important medical event terms list (MedDRA version 22.0)

MedDRA Code	PT Name	SOC Name	Comment	Added in 22.0	Primary SOC Change
10082297	Blood loss anaemia	Blood and lymphatic system disorders	Blood loss, a synonym for hemorrhage, can disrupt blood flow and cause damage to vital organs. It meets the criteria for	X	
10082480	Cardiohepatic syndrome	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IME list for conditions leading to important organ alterations.	X	
10082089	Frederick's syndrome	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IME list for relevant terms for cardiac arrhythmias. Frederick's	X	
10082054	Neonatal bradyarrhythmia	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IME list for relevant terms for cardiac arrhythmias. A similar term,	X	
10082055	Neonatal tachyarrhythmia	Cardiac disorders	New PT in v22.0. This term meets the inclusion criteria for the IME list for relevant terms for cardiac arrhythmias. A similar term,	X	
10082380	Aberrant aortic arch	Congenital, familial and genetic disorders	Aberrant aortic arch configurations can disrupt blood flow and cause damage to vital organs. Even when these aberrant	X	
10082546	Congenital arterial occlusion	Congenital, familial and genetic disorders	Arterial occlusive disease can produce ischemia or infarction of vital organs. Even when arterial occlusive disease is congenital, it	X	
10082343	Congenital supraventricular tachycardia	Congenital, familial and genetic disorders	Tachyarrhythmias can disrupt blood flow and cause damage to vital organs. Even when tachyarrhythmia is congenital, it can be a	X	
10082084	Grey matter heterotopia	Congenital, familial and genetic disorders	Grey matter heterotopia is caused by clumps of grey matter located in the wrong part of the brain and is characterized as a	X	

22.0 IME List | Deleted PTs | Deleted Surgical PTs

Term Level	Term Text	Primary SOC
PT	Acute generalised exanthematous pustulosis	Skin and subcutaneous tissue disorders
PT	Acute hepatic failure	Hepatobiliary disorders
PT	Agranulocytosis	Blood and lymphatic system disorders
PT	Anaphylactic shock	Immune system disorders
PT	Anaphylactoid shock	Immune system disorders
PT	Angiolymphoid hyperplasia with eosinophilia	Skin and subcutaneous tissue disorders
PT	Aplasia pure red cell	Blood and lymphatic 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