PREPARING FOR CHANGE

2018 26-28 SEPT

SACRA
SOUTH AFRICAN CLINICAL RESEARCH ASSOCIATION

8th Clinical Research Conference

Reading and adapting to industry trends

IMPROVING MONITORING EFFICIENCY BY UNDERSTANDING THE ROLE OF DATA MANAGEMENT & PRE-EMPTING QUERIES

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Objective:

To provide guidance to operations staff on:

- Reporting of Medical History, Adverse Events and Concomitant Medication for coding purposes
- Study Drug Administration reporting
- Laboratory data collection

to aid data quality and minimise queries

Dictionary.com definition of *Quality: character with respect to fineness, or grade of excellence*

What is Good Quality Data?

ALCOA

A : Attributable
L : Legible
C : Contemporaneous
O : Original
A : Accurate

What is missing?....

C : Complete

(ICH GCP E6 R2 #4.90)

Success of a trial is dependant on data quality

Getting Started…..

KNOW YOUR PROJECT

Know your protocol and eCRF guidelines

Specific requirements of your study re:

- Adverse Event Capture
- Concomitant Medications (trade/ generic names)
- Medical History

CRF Edit Specifications

dataset	ecnum	visit	field	multi	descript	logic	stdtxt
DM	A1	1	SITEID		Missing / Invalid Site Number	SITEID < 3 characters	THE SITE NUMBER IS MISSING OR INVALID. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A2	1	SUBJID		Missing / Invalid Subject Number	SUBJID < 3 characters	THE SUBJECT NUMBER IS MISSING OR INVALID. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A3	1	INITIALS		Missing/Invalid Subject Initials	INITIALS < 3 characters	THE SUBJECT INITIALS ARE MISSING OR INVALID. USE A DASH (-) FOR THE MIDDLE INITIAL IF NECESSARY. IF YOUR SITE IS IN GERMANY OR THE NETHERLANDS YOU MUST USE (XXX). PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A4	1	VISDT		Invalid Visit Date	VISDT < 11 characters	THE VISIT DATE IS MISSING OR INVALID. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A5	1	VISDT		Visit date out of range	VISDT < 14/SEP/2015	THE VISIT DATE IS OUT OF RANGE FOR THE STUDY. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A6	1	DSSTDAT		Invalid Date of Informed Consent	DSSTDAT < 11 characters	THE CONSENT DATE IS MISSING OR INVALID. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A7	1	DSSTDAT		Consent date > Visit date	DSSTDAT > 1;DM;VISDT	CONSENT DATE OCCURRED AFTER VISIT DATE. PLEASE CORRECT OR CONFIRM AS NECESSARY.
DM	A8	1	DSSTDAT		consent date out of range.	DSSTDAT < 14/SEP/2015	THE CONSENT DATE IS OUT OF RANGE FOR THE STUDY. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A9	1	BRTHDAT		Invalid Date of birth	BRTHDAT < 11 characters	THE DATE OF BIRTH IS MISSING OR INVALID. PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A10	1	BRTHDAT		Invalid Date of birth	BRTHDAT > 14/SEP/2020	THE DATE OF BIRTH IS OUT OF RANGE (MUST BE AT LEAST 18 PER PROTOCOL). PLEASE MAKE THE APPROPRIATE CORRECTION.
DM	A11	1	AGE		AGE Missing or Invalid.	AGE NE 2 characters	AGE IS MISSING OR INVALID. PLEASE PROVIDE THE APPROPRIATE RESPONSE.
DM	A12	1	AGE		AGE Invalid	AGE = 17&99	THE AGE IS OUT OF RANGE (MUST BE AT LEAST 18 PER PROTOCOL). PLEASE MAKE THE APPROPRIATE CORRECTION.

WHY CODE?

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Reading and adapting to industry trends

- Facilitates
  Storage, Retrieval, Analysis & Presentation of Data
- Provides structure for flexible data retrieval & analysis
- Accuracy of initial coding determines the accuracy of analysis

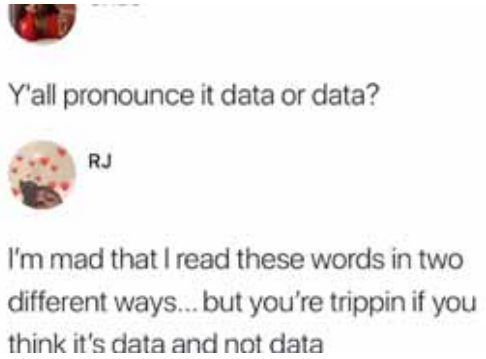
Eg: sore head, headache, head hurts >> would be coded to HEADACHE

Data Coding:

- **Most data entered on CRFs are "coded" in some form**
- **Some coding is performed by investigators at point of data entry**
  - **eg. AE severity assigned numeric codes : 1= mild, 2= moderate, 3 = severe.**
- **Other coding of text data is performed by the sponsor company after data collection**
  - **Manual coding**
  - **Automatic coding**
- **Relies on clear, initial data**
- **What is evident to the site/ Investigator at point of data entry may not be clear to the coder at point of coding**
- **Only the verbatim term can be coded, DM is not able to interpret or draw information from other sources**

THE ROLE OF THE CRA

The CRA



Study database:

Data Quality In = Data Quality Out

- Responsible for working with the site to ensure appropriate data is captured in the source / database
- Monitoring is critical to ensure good data quality

DATA MANAGEMENT TOOLS

- MedDRA – AE terms/ Medical History
- WHO DDE – Concomitant Medications

Adverse Events

MedDRA

(**Med**ical **D**ictionary for **R**egulatory **A**ctivities)

Standardise event terminology used in clinical research – AEs/ Medical History

"MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation."

MedDRA version 17

What does MedDRA Code?

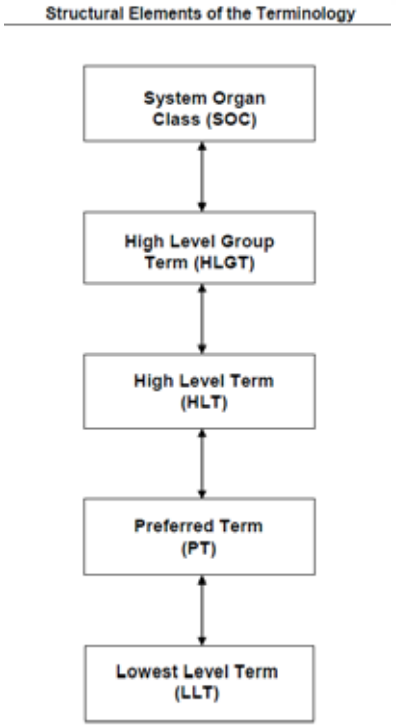
- **Signs (i.e. Redness)**
- **Symptoms (i.e. Dizzy)**
- **Diseases (i.e. AIDS)**
- **Diagnoses (i.e. Hepatic failure)**
- **Therapeutic indications (i.e. Congestive heart failure)**
- **Names and qualitative results of investigations (i.e. Decreased haemoglobin)**
- **Surgical and medical procedures (i.e. Hysterectomy)**
- **Medical, social, and family history (i.e. Alcoholism)**

MedDRA Coding

- Each MedDRA term is assigned an 8 digit numeric code

- Allows Global studies to be coded in a centralised database

MedDRA Hierarchical Structure



- **SOC (26)**
- **HLGT (334)**
- **HLT (1,720)**
- **PT (20,599)**
  - LLT is linked to only one
- **LLT (72,637)** - provides maximum specificity

System Organ Classes (SOC) *(26)*

- Blood and lymphatic system disorders
- Cardiac disorders
- Musculoskeletal and connective tissue disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Psychiatric disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

Output Tables

System Organ Class / Preferred Term (PT)	Arm 1: (N=26) Nr(%) of Subjects	Arm 1: (N=26) Nr of MHs	Arm 2: (N=26) Nr(%) of Subjects	Arm 2: (N=26) Nr of MHs
Nr of subjects reporting at least one Medical History	25 (96.15%)	242	26 (100.00%)	281
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (3.85%)	1	1 (3.85%)	2
ANAEMIA	1 (3.85%)	1	0	0
INCREASED TENDENCY TO BRUISE	0	0	1 (3.85%)	1
IRON DEFICIENCY ANAEMIA	0	0	1 (3.85%)	1
CARDIAC DISORDERS	7 (26.92%)	14	10 (38.46%)	14
AORTIC VALVE DISEASE	1 (3.85%)	1	0	0
AORTIC VALVE STENOSIS	1 (3.85%)	1	0	0
ARRHYTHMIA	1 (3.85%)	1	0	0
ATRIAL FIBRILLATION	3 (11.54%)	3	3 (11.54%)	3
ATRIAL FLUTTER	0	0	0	0
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	0	0	0
BRADYCARDIA	1 (3.85%)	1	1 (3.85%)	1
BUNDLE BRANCH BLOCK LEFT	0	0	1 (3.85%)	1
BUNDLE BRANCH BLOCK RIGHT	1 (3.85%)	1	0	0
CARDIAC FAILURE CONGESTIVE	0	0	0	0

		Arm 1: (N=26)	Arm 2: (N=26)
Age(Years)*	n	26	26
	Mean	70.50	68.58
	Median	72	69.5
	SD	11.176	11.518
	Minimum	35	40
	Maximum	93	87
Gender n(%)	Male	23 (88.46%)	21 (80.77%)
	Female	3 (11.54%)	5 (19.23%)
Race n(%)	White	26 (100.00%)	25 (96.15%)
	African American	0	0
	Asian	0	1 (3.85%)
	Native Hawaiian or Pacific Islander	0	0
	American Indian	0	0
	Alaskan Native	0	0
	Other	0	0
Ethnicity n(%)	Hispanic or Latino	1 (3.85%)	2 (7.69%)
	Not Hispanic or Latino	25 (96.15%)	24 (92.31%)

*Age Calculated at Date of Baseline; SD: Standard Deviation.

AE Terminology is Important

Query 'Please update the AE term, please use acceptable medical terminology. ' answered with 'not otherwise specified- this was the term used by the patient.' (Site from CRA).
User opened query 'Please update the AE term, please use acceptable medical terminology. ' (Site from CRA).
DataPoint Verified.
User entered 'A mass was found on the Pancreas'

DEATH – How to report

- Death is usually reported as the ‘outcome’ of an AE rather than an AE itself.
- Death may also be captured in the severity grading. Eg. CTC grading 5 = death
- Refer to protocol or CRF completion guidelines in case there are study specific requirements

AE with Outcome 'DEATH'

VIEDOC

SUBJECT ID **S10-010**

INIT **CLG** GENDER **Male** DATE OF BIRTH **03 Apr 1919**

INFORMED CONSENT **04 Feb 2015** COHORT - PROTOCOL VERSION AT ENROLMENT **Protocol Amendment V4.0**

Adverse Events

Add

Line # 2

Adverse Event: Myocardial Infarction

Start Date: 2 Apr 2015

Ongoing: (•) No ( ) Yes

Stop Date: 2 Apr 2015

Serious Adverse Event? ( ) No (•) Yes

Action Taken
- [ ] None
- [ ] Study medication dose changed
- [ ] Study medication permanently discontinued
- [ ] Symptomatic therapy
- [ ] Hospitalisation/Prolonged Hospitalisation
- [x] Other ↓

Patient discontinuec

CTC Grade
- ( ) 1 Mild
- ( ) 2 Moderate
- ( ) 3 Severe
- ( ) 4 Life threatening or disabling
- (•) 5 Death related to AE

Causality (Relationship to study drug): Possible

Outcome: Death

Please complete the Serious Adverse Event SAE form and provide it to Novotech within 24 hours of the Investigators knowledge of the event.

Save Cancel

Multi-axial Terminology

- Multi-axial = the representation of medical concept in multiple SOCs
  - Allows grouping by different classifications & retrieval/ presentation via different data sets.
  - Preferred Terms can be mapped to multiple System Organ Classes (SOCs) - eg. Influenza

Eg: Influenza

SOC = Respiratory, thoracic and mediastinal disorders

HLGT = Respiratory tract infections

HLT = Viral upper respiratory tract infections

SOC = Infections and infestations

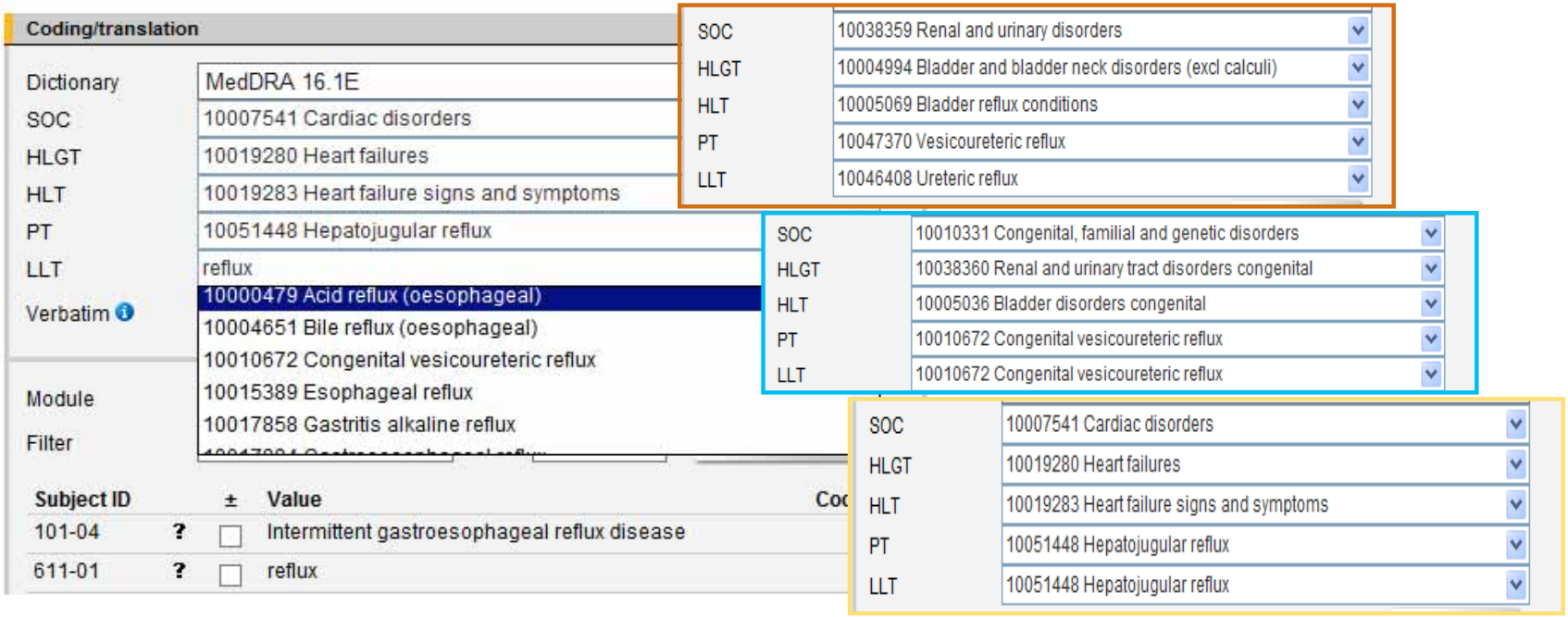
HLGT = Viral infectious disorders

HLT = Influenza viral infections

PT = Influenza

Requirement to Define

A term can have multiple different codes assigned based on the LLT



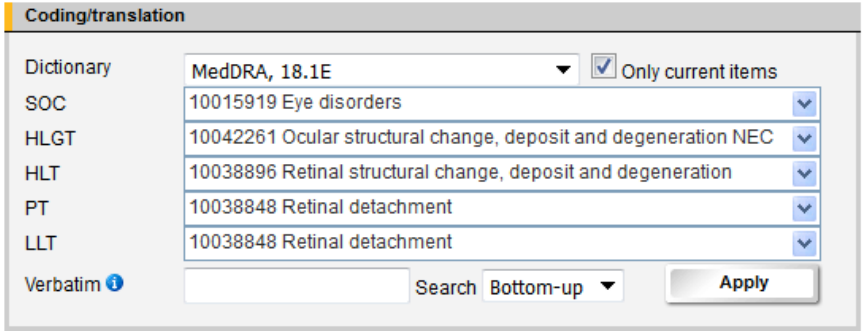
AE “due to fall”

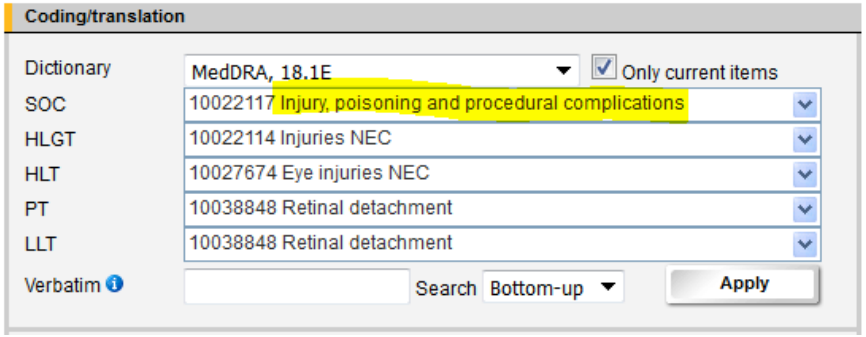
- AE reported as ‘Retinal detachment due to fall’
- Cause of retinal detachment - ‘due to fall’ assists with coding.

There are two SOC options for ‘Retinal detachment’

1)Eye disorders

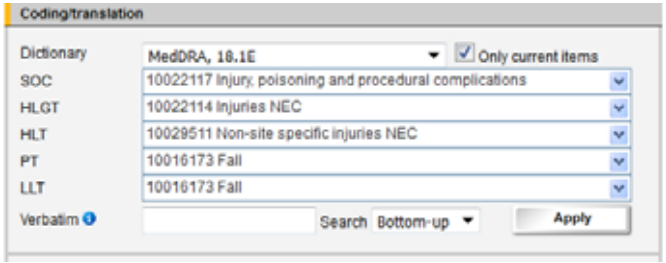
2)Injury, poisoning and procedural complication





Recording ‘Fall’ as an AE

- Confirm with the sponsor or refer to protocol/ CRF completion guideline if ‘fall’ also need to be recorded as an AE.
- As a general rule, if in doubt, over report and also record ‘fall’ as a separate AE.



Avoiding Potential Problems

(a team effort)

‘Congestion’ as reported term

- Congestion (nasal, liver, sinus, pulmonary?)

‘Pain’ as reported term

- (gastric ulcer pain or genito-urinary pain?)

‘Runny nose, cough, body aches as reported term

- (Flu?)

Example: Abbreviations

- **MI**

  myocardial infarction or mitral incompetence?

- **GU pain**

  gastric ulcer pain or genito-urinary pain?

- **Decreased BS**

  breath sounds, bowel sounds or blood sugar?

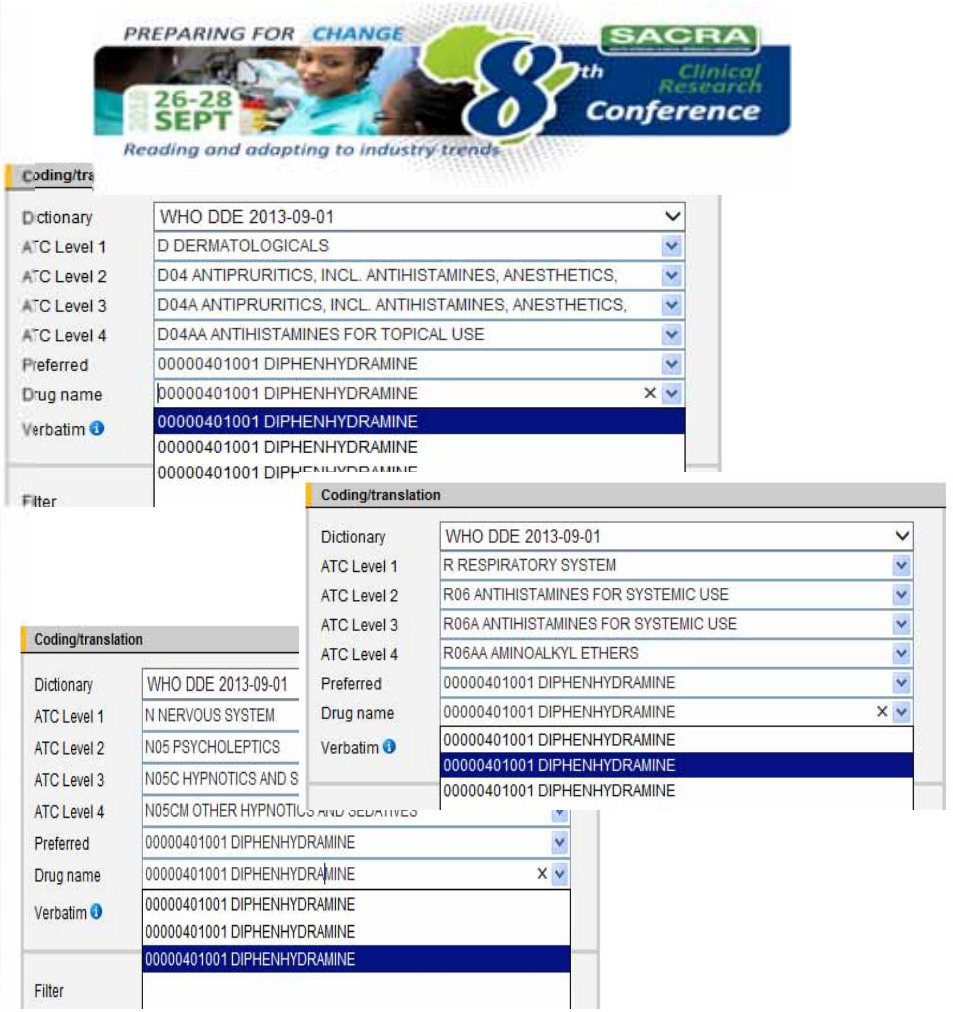
Concomitant Medications (Conmeds)

World Health Organisation Drug Dictionary Enhanced (WHO DDE)

- Translates a drug name to useful information
  - for coding and analysis of drug safety data –pre- & post- marketing.
- World's most comprehensive dictionary of medicinal product information.
  - Each medicinal product has a drug code as well as a unique Medicinal Product ID
- Coding per Anatomical, Therapeutic & Chemical (ATC) groupings
- Used by pharmaceutical companies, CROs and drug regulatory authorities for identifying
  - Ø drug names
  - Ø active ingredients and
  - Ø therapeutic use, in the course of their drug safety surveillance.

ATC Coding – Why indication matters

- Different indications will result in different ATC classification
- *Ensure site has provided as much information as possible in source/ eCRF*



TIPS TO PREVENT MOST COMMONLY RAISED CODING QUERIES

- Record medical diagnosis or condition rather than signs or symptoms using medical terms
- Check correct indications are reported for conmeds
- Avoid using terms in local language
- Avoid abbreviations as these can be misinterpreted
- Avoid vague descriptors such as “fuzzy” or “weird”

TIPS……

Ensure specific information is reported

- "Left wrist edema" (coded as Peripheral edema)
- More specific - "Injection site edema left wrist" (coded as Injection site edema or Infusion site reaction)

Review your guidelines - are trade names or generic names required?

- If not specified use generic name for 2 or less active ingredients. For greater than 2 actives use trade name (confirm with eMIMS)

Other important data points

Study Drug Administration

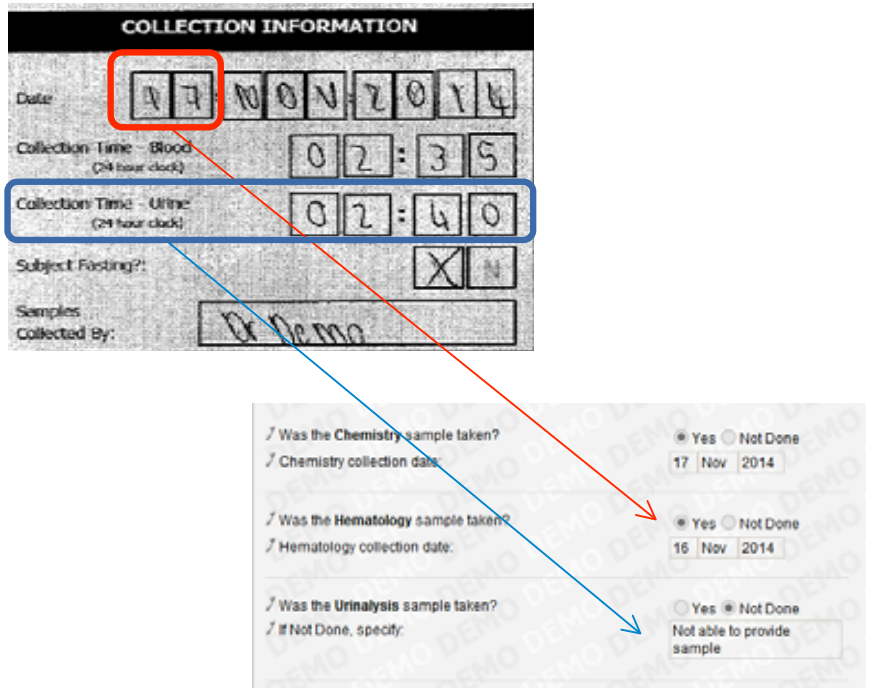
Critical for analysis to have accurate data

You can help by checking:

- Dosing dates in chronological order
- No unexplained gaps in dosing schedule
- Protocol deviations and non-compliance are recorded

Laboratory Data Forms

- Generates majority of data queries
- Database vs. Source
  - Collection dates and times
  - Dates correspond with study visits
  - Sample collected vs. reported



Summary

- Clinical and DM departments are parts of the same team
- Stay in contact
- *WHAT IS NOT RECORDED IS NOT DONE*

USEFUL RESOURCES and REFERENCES

- Common Terminology Criteria for Adverse Events (CTCAE) v4.03
  - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- MIMS
- MedDRA coding dictionary
  - http://www.meddra.org
  - MedDRA Coding Basics http://www.meddra.org/sites/default/files/page/documents_insert/6275-1700_coding_basics.pdf
- WHO DDE
  - http://www.umc-products.com/graphics/26793.pdf

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