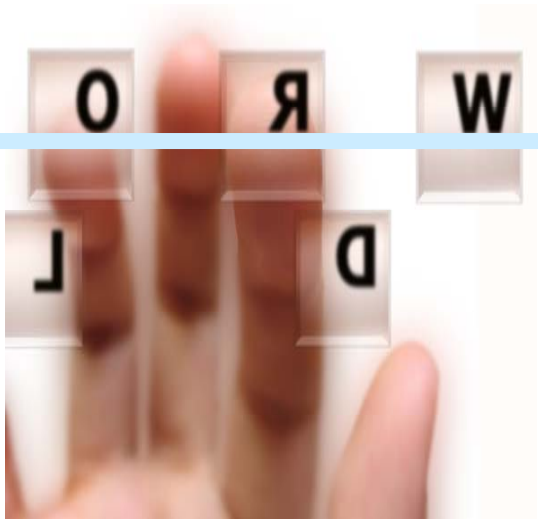



# AE/SAE Reporting and Coding

**Yu Zhang**
**Roche**

1 AE/SAE reporting

2 Coding


# AE/SAE Reporting

# What is AE?

An AE (Adverse Events) is any unfavorable and unintended medical occurrence/sign (including an abnormal laboratory finding), symptom or disease in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

# What is AE?(Cont.)

- Occurrence/sign, symptom or disease
- Administered a pharmaceutical product
- No need causal relationship

# ADR (Adverse Drug Reaction )

- All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

# Why collect AE?

- Patient
- Regulatory
- Pharama ??

- AE＝Bad？

# AE collection form (example)

- Name of AE
- Onset date
- Intensity (Grade)
- Relationship with study medication
- Study medication adjustment
- Whether or not a SAE
- Outcome
- Resolve date
- Treatment for AE
- Comments

# Adverse event or intercurrent illness

Name of event: _____

Is this a serious adverse event [2](see definition in protocol)?

☐ 0 No ☐ 1 Yes → *complete SAE form within one working day of occurrence and telefax immediately to the sponsor*

Date of onset |__|__|__|__|__|__|
dd mm yy

Test drug adjustment[4]

☐ 1 None

☐ 2 Dosage modified/interrupted

☐ 3 Discontinued → *complete study completion section*

Intensity [5]

☐ 1 Mild

☐ 2 Moderate

☐ 3 Severe

☐ 4 Life-threatening

Relationship to test drug[6]

☐ 1 Probable

☐ 2 Possible

☐ 3 Remote

☐ 4 Unrelated

Outcome[7] ☐ 1 Resolved-no sequelae

☐ 2 Resolved-with sequelae

☐ 3 Unresolved

☐ 4 Death

→ Date Resolved |__|__|__|__|__|__|
dd mm yy

Was treatment given for this event?

☐ 0 No ☐ 1 Yes → *record any treatment or medical procedure below*

Comments on AE _____

| | Generic name of treatment or procedure[8]* | start date dd/mm/yy | end date[9] dd/mm/yy | Ongoing at end of study |
|---|---|---|---|---|
| 1 | _____ | __/__/__ | __/__/__ | ☐ |
| 2 | _____ | __/__/__ | __/__/__ | ☐ |
| 3 | _____ | __/__/__ | __/__/__ | ☐ |
| 4 | _____ | __/__/__ | __/__/__ | ☐ |

*** If there are more than 4 treatments please mark ☐**

**And complete additional loose-leaf pages for treatments of AE**

# AE Term

- Diagnosis
- Symptom (location)
- Sign (location)
- One Events one AE
- Check Writing
- Do not use abbreviation

# Grade of AE

National Cancer Institute Common Terminology Criteria for Adverse Events

| CTCAE Grade | Equivalent To: | Definition |
|---|---|---|
| Grade 1 | Mild | Discomfort noticed but no disruption of normal daily activity |
| Grade 2 | Moderate | Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the subject |
| Grade 3 | Severe | Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk. |
| Grade 4 | Life threatening/disabling | An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival. |
| Grade 5 | Death | AE resulting in death |

# Relationship with AE

- If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

# Relationship with AE

**Yes** criteria **:**

- ✓Reasonable temporal association with drug administration
- ✓Known response pattern to suspected drug
- ✓Disappears or decreases on cessation or reduction in dose
- ✓Reappears on rechallenge

# Relationship with AE

**No** criteria **:**

- ✓It does not follow a known pattern of response to the suspected drug.
- ✓It does not reappear or worsen when the drug is re-administered.
- ✓It does not follow a reasonable temporal sequence from administration of the drug.

# Relationship options

- Unrelated
- Remote
- Possible
- Probable

# Study medication adjustment

- None
- Adjusted/Interrupted
- Discontinued

# Outcome and resolve date

- Resolved (should record resolve date)
- Unresolved
- Death

# Exercise

一个病人在2008年10月1日注射研究用药过程中，出现了头疼的症状。医生觉得症状比较严重，是三级的不良事件，判断此次病人出现头疼与研究用药高度相关。于是医生中断了病人的注射，同时给病人服用了A药以治疗头疼。持续服用A药后，头疼症状于2008年10月3日消失。

# SAE?

Criteria:

- Fatal (results in death)
- Life-Threatening
- Hospitalization or prolong hospitalization
- Anomaly/birth defect
- Disability/incapacity

- is medically significant or requires intervention to prevent one or other of the outcomes listed above

# SAE reporting

- Report to the sponsor
  - 1 working day
  - Use SAE reporting form
- Report to SFDA

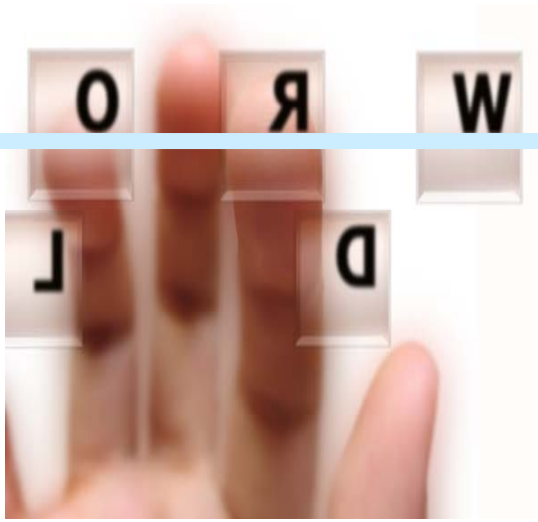
Microsoft Word Document

- Also Record in CRF

# SAE reporting to sponsor

Essential elements:

1) Protocol number
2) Patient Identifier: (patient ID, initial, birthday, gender)
3) Event term
4) Onset date
5) Drug name
6) Possible causes of event
7) Event seriousness

# AE/SAE Analysis

# AE/SAE analysis

- Summary of AE by group
- Summary of AE by Organ System by group
- Summary of grade 3/4 AE by Organ System by group
- Summary of related AE by Organ System by group
- Summary of SAE by group
- SAE listing
- Treatment for AE

➢ P-value is not used for safety analysis

# 表 2_1 不良事件总结

| 项目 | 研究药物 | | 对照药物 | |
|---|---|---|---|---|
| | 例数 | 发生率(%) | 例数 | 发生率(%) |
| 样本量 | 999 | | 999 | |
| 不良事件（AE） | 999 | 99.9 | 999 | 99.9 |
| 不良反应（ADR）* | 999 | 99.9 | 999 | 99.9 |
| 死亡的不良事件 | 999 | 99.9 | 999 | 99.9 |
| 导致退出的不良事件 | 999 | 99.9 | 999 | 99.9 |
| 导致注射中断的不良事件 | 999 | 99.9 | 999 | 99.9 |
| 严重不良事件(SAE) | 999 | 99.9 | 999 | 99.9 |
| 严重不良反应(SAR)* | 999 | 99.9 | 999 | 99.9 |

# 表 2_2_1 按照器官系统分类的不良事件的统计描述

| 器官系统（System organ class） | 不良事件（Preferred term） | 研究药物 | | 对照药物 | |
|---|---|---|---|---|---|
| | | 例数 | (%) | 例数 | (%) |
| 样本量 | | 999 | | 999 | |
| XXXXXXXXXXX | 至少出现一次不良事件患者总数 | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| XXXXXXXXXXXXX | 至少出现一次不良事件患者总数 | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |
| | XXXXXXXXXXXXXXXXX | 99 | ( 99.9 ) | 99 | ( 99.9 ) |


# SAE reconciliation

# Purpose of SAE reconciliation

- Compare SAE for one study in Clinical database with SAE in Safety database to ensure the quality of SAE data.

- DM will combine two SAE tables from different database into a SAE reconciliation report and send to scientist to review.

# SAE reconciliation process

- Generate SAE reconciliation report

  (Include patient ID, site number, birthday, SAE verbatim term, SAE prefer term, Onset date, relationship with study medication)

- Review SAE reconciliation report

- Resolve the discrepancy

# SAE reconciliation

- Number of SAE (study/patient)
- Prefer term
- Relation with study medication
- Start date

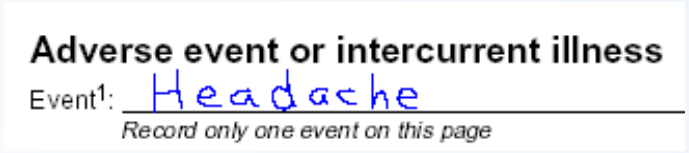

# Coding Overview

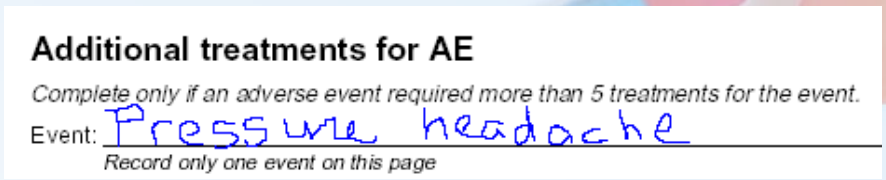
# Why?

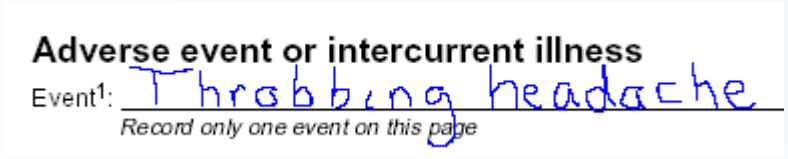
- To facilitate the aggregation of verbatim reports into medically meaningful groupings so that they can be reviewed, analysed and communicated to the regulatory authorities.

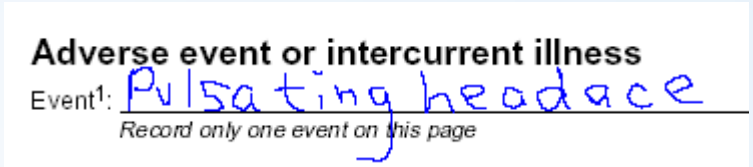
- To ensure the accurate, unbiased & consistent classification of CRF verbatim terms as reported by the investigators

# Why Do Medical and Drug Terms Need to Be Classified?




Investigators report the same medical and treatment terms (called verbatim terms) in many different ways on the CRF. In order to compare the frequency of adverse events in drug treatment versus non treatment groups the terms need to be classified into standardized terminology.

# What?

- AE term
- Treatment Name

# How?

- Medical events –

  MedDRA (Medical Dictionary for Regulatory Activities)

- Treatments and procedures –

  INN (International Non-proprietary Name)
  WhoDrug (WHO Drug Dictionary)

- Terms that match a dictionary term are classified automatically

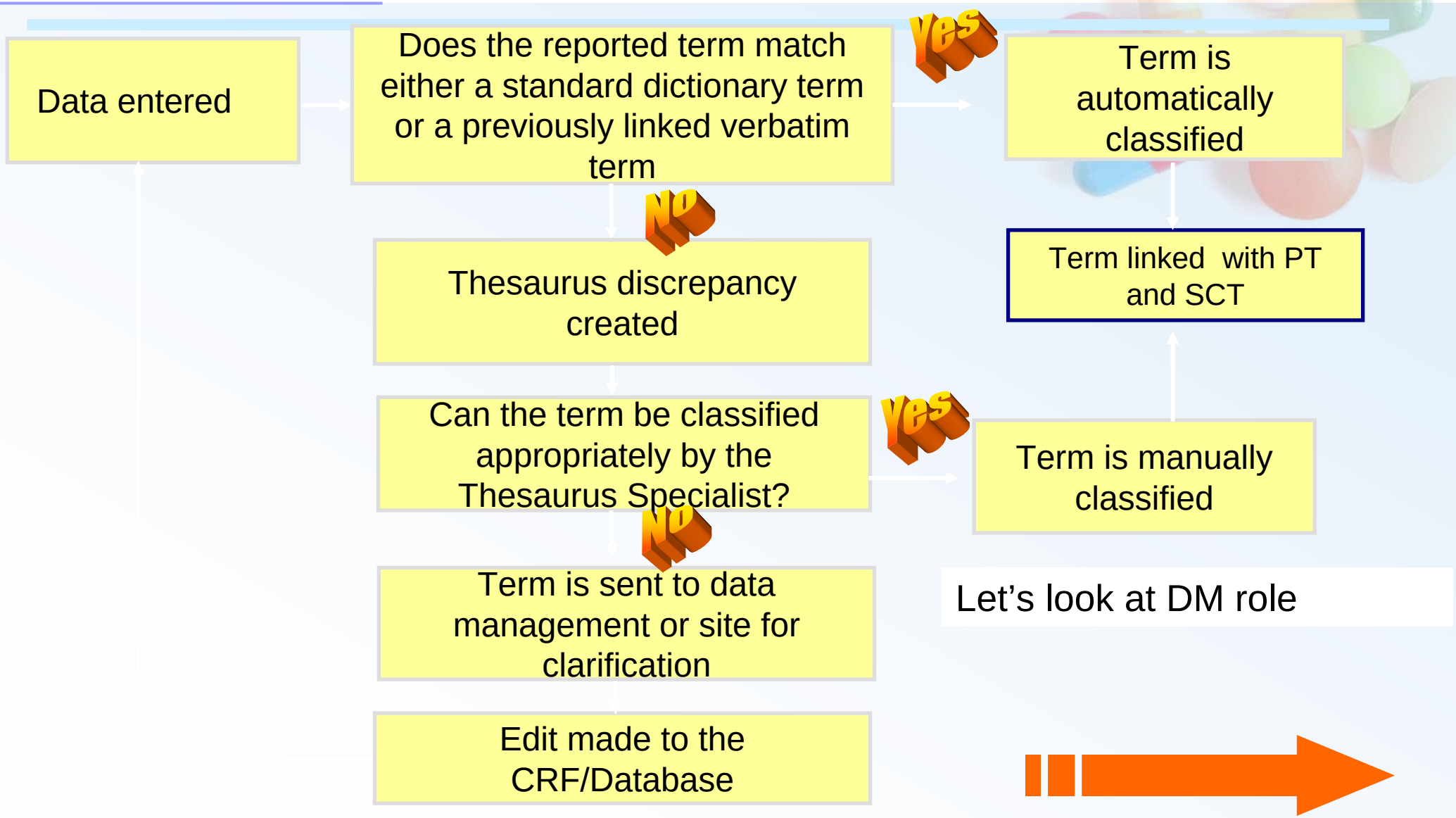
# When are terms manually classified?

- Terms that do not find an exact match among the terms in the dictionaries become discrepancies
- Discrepancies for this terms will need Thesaurus review and coding

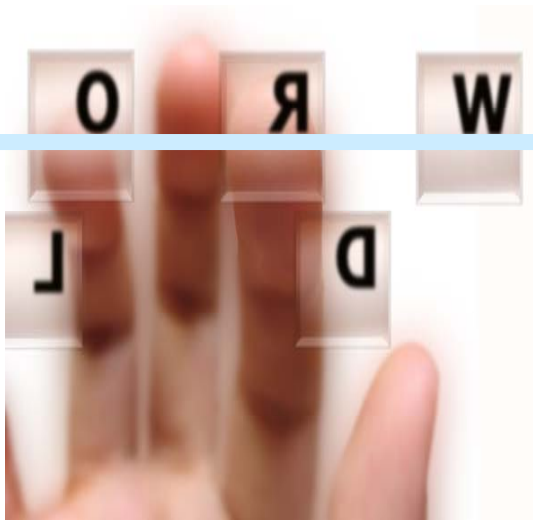
# Coding Discrepancy

- Pain
- Nausea & Vomiting
- Headche
- DIC
- Hemoglobin

# Classification Process(AE term)



# The 2nd Clinical Data Management Training

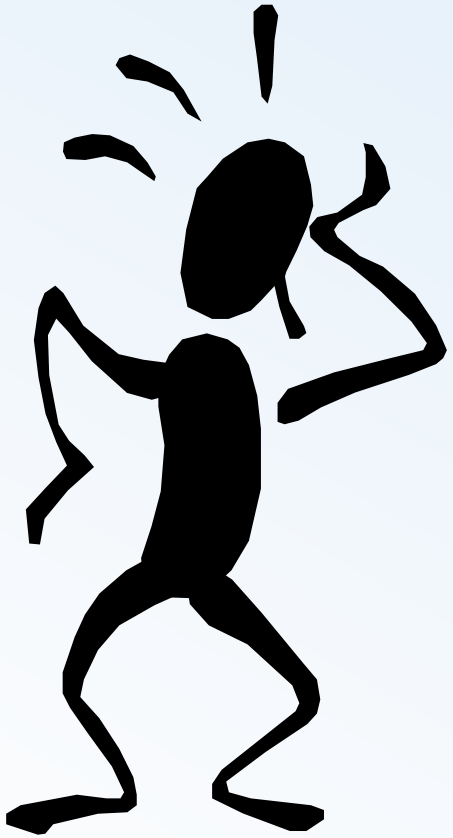
# MedDRA Dictionary

# Outline of this Session

- History of MedDRA
- MedDRA Scope & Structure
- Current status of MedDRA

MedDRA

Meddra



MEDDRA

MEdDRA

MedDRa

MedrRA

# History of MedDRA

- 1989: UK Medicines Control Agency (MCA) identifies need for a single medical terminology for drug regulation to support its new computer databases
- 1993: European Community identifies identical need to support its drug regulatory system. Wider applicability of MCA medical terminology is assessed

# History of MedDRA (cont.)

- 1994: Working Party reviews and amends MCA terminology, now called MEDDRA (Medical Dictionary for Drug Regulatory Affairs). ICH adopts MEDDRA

- 1996: MedDRA 1.5 international Beta test version released

# History of MedDRA (cont.)

- 1997: ICH agrees the ‘implementation version’ (v2.0) and adopts new name: the Medical Dictionary for Regulatory Activities (MedDRA). Terms in MedDRA derive from WHO-ART, COSTART, HARTS, ICD-9, ICD 9-CM
- 1998: Maintenance and Support Services Organization (MSSO) is selected for 5 years by ICH

# History of MedDRA (cont.)

- Early 1999: Services and distribution begin (with v2.0)
- Each MedDRA term receives an unique 8-digit numeric code to facilitate electronic transmission. This is sequential without inherent meaning

# Scope of MedDRA

## Excluded

- Patient demographic terms
- Drug product terms
- Device failure terms
- Clinical trial study design terms

## Included

**Diseases**

**Diagnoses**

**Signs & Symptoms**

**Therapeutic indications**

**Investigation names & qualitative results**

**Medical & surgical procedures**

**Medical and social history**

Population-led qualifiers

Numerical test results

Severity descriptors

Diagnostic products

Equipment and device terms

# MedDRA Structure

## 5 Levels

- SOC: System Organ Class
  - HLGT: High Level Group Term
    - HLT: High Level Term
      - PT: Preferred Term
        - » LLT: Lowest Level Term

# Basic Structure Example

SOC = Psychiatric disorders

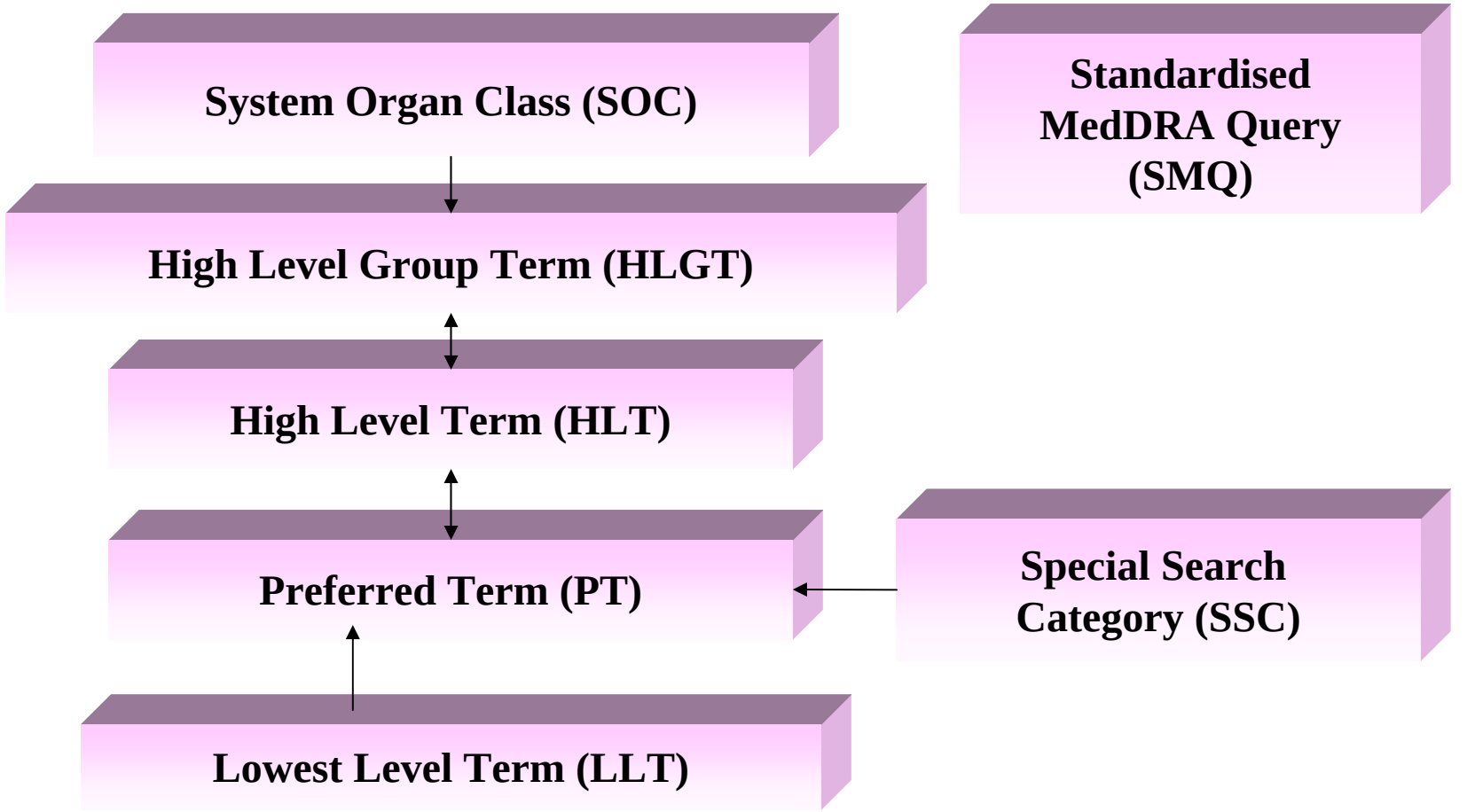
HLGT = Dissociative disorders

HLT = Dissociative states

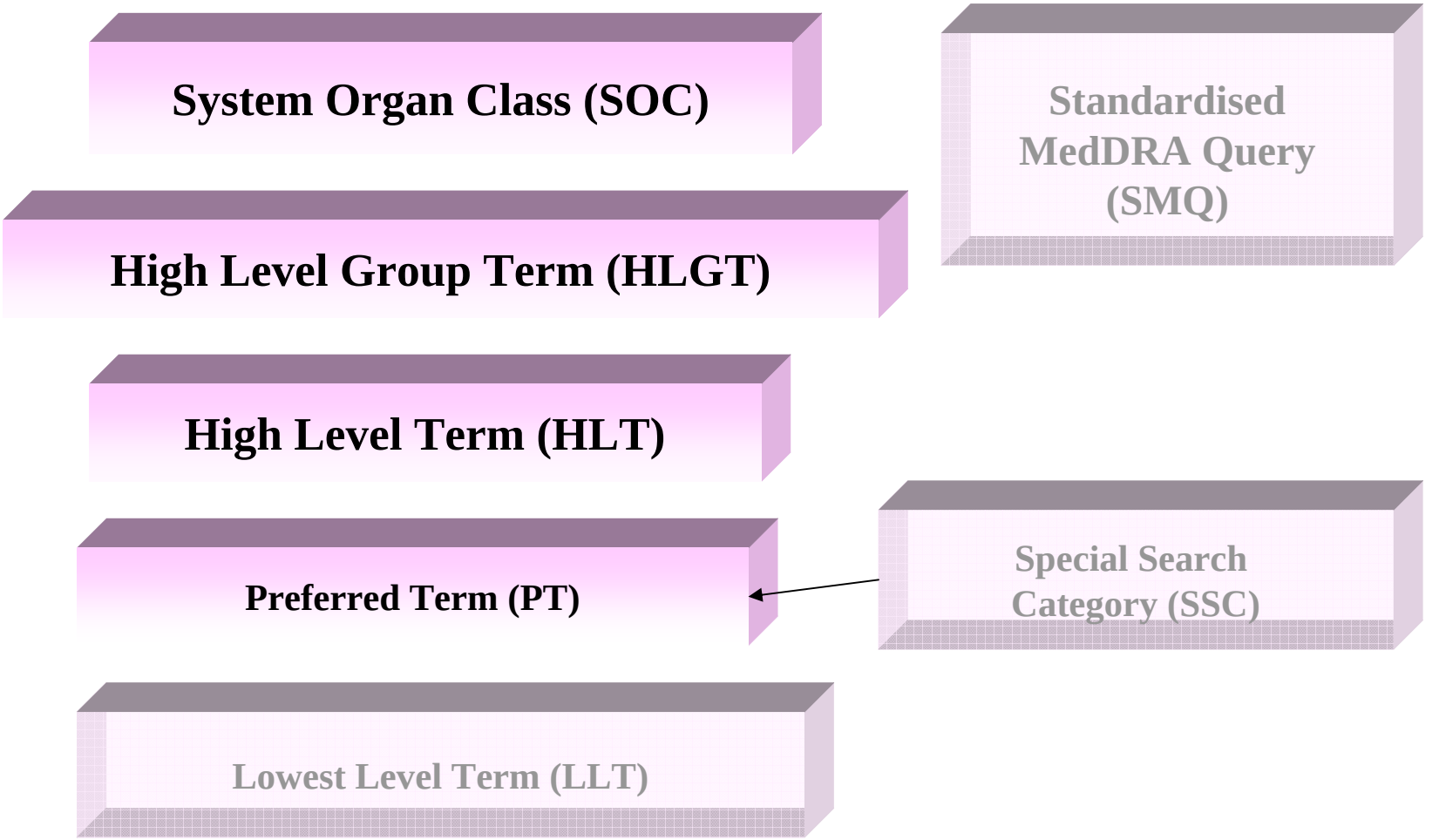
PT = Dissociative identity disorders

LLT = Multiple personality disorders

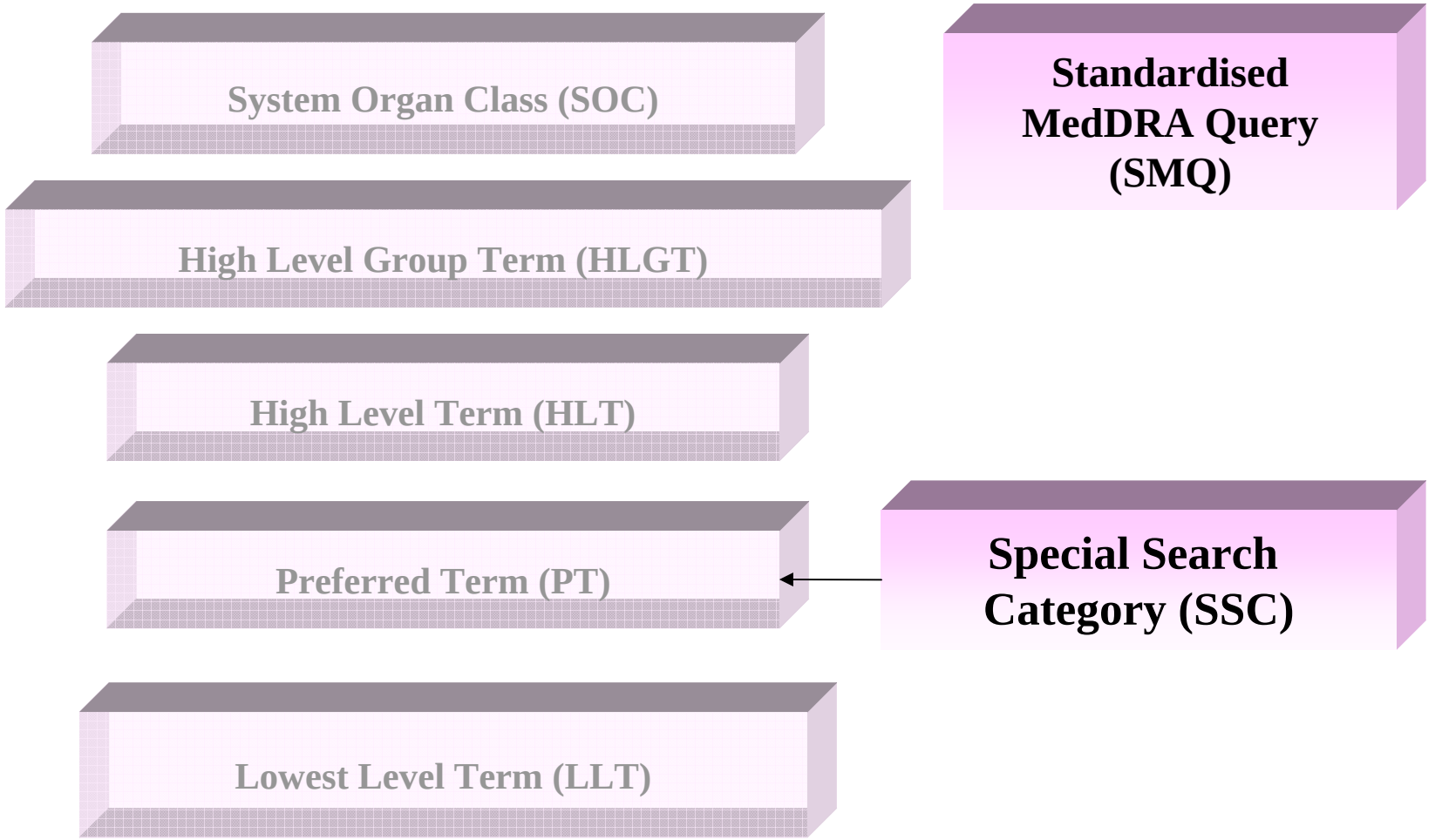
# Terminology



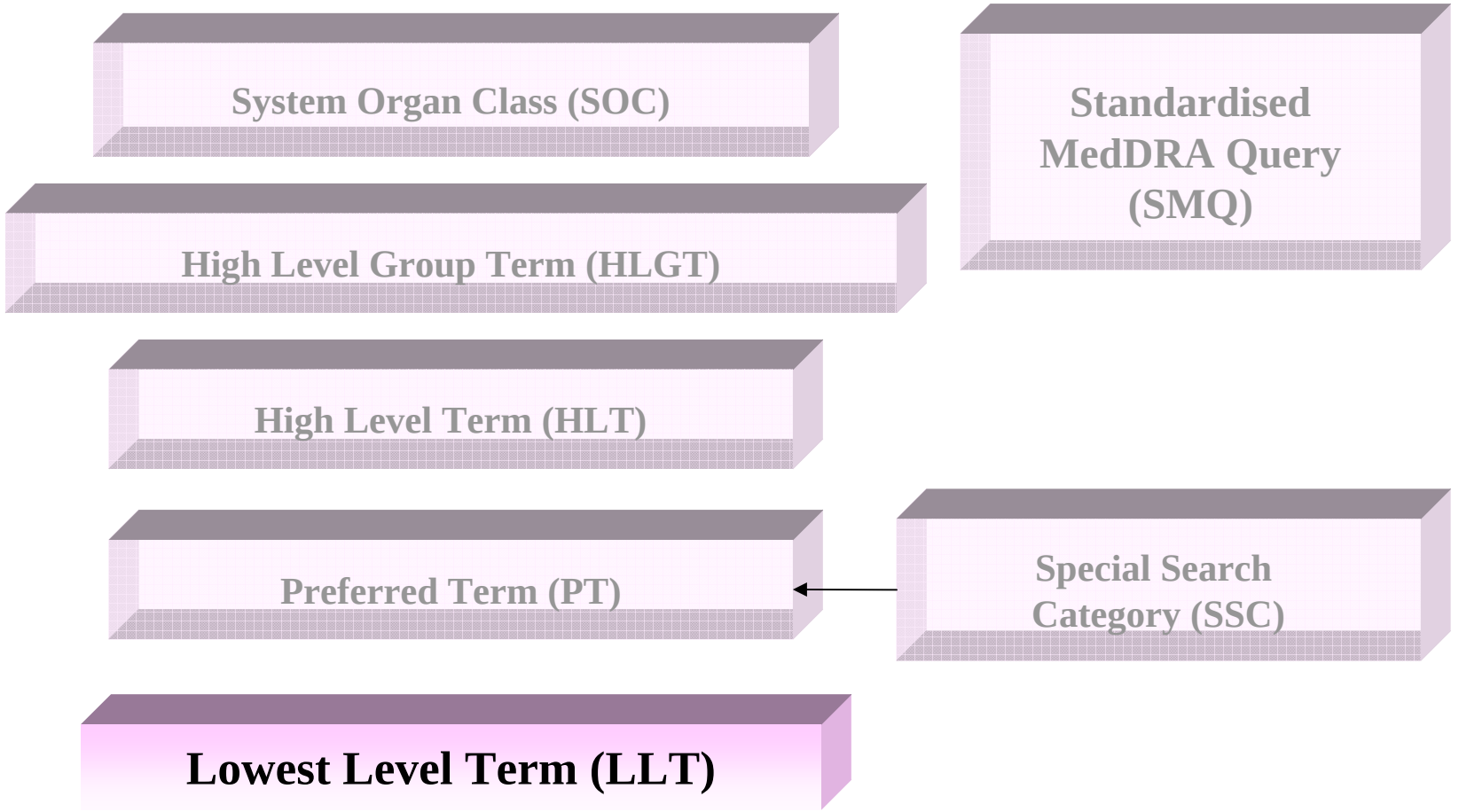
# Analysis & Reporting Terms



# Query Terms


System Organ Class (SOC)
High Level Group Term (HLGT)
High Level Term (HLT)
Preferred Term (PT)
Lowest Level Term (LLT)
Standardised MedDRA Query (SMQ)
Special Search Category (SSC)

# Coding Terms



# The 26 MedDRA SOCs

**Blood - Blood and lymphatic system disorders**

**Card - Cardiac disorders**

*Cong - Congenital, familial and genetic disorders*

**Ear - Ear and labyrinth disorders**

**Endo - Endocrine disorders**

**Eye - Eye disorders**

**Gastr - Gastrointestinal disorders**

**Genrl - General disorders and administration site conditions**

*Hepat - Hepatobiliary disorders*

**Immun - Immune system disorders**

**Infec - Infections and infestations**

*Inj&P - Injury, poisoning and procedural complications*

**Inv - Investigations**

**Metab - Metabolism and nutrition disorders**

**Metab - Metabolism and nutrition disorders**

*Musc - Musculoskeletal, connective tissue and bone disorders*

*Neopl - Neoplasms benign, malignant and unspecified (incl cysts and polyps)*

**Nerv - Nervous system disorders**

**Preg - Pregnancy, puerperium and perinatal conditions**

**Psych - Psychiatric disorders**

**Renal - Renal and urinary disorders**

**Repro - Reproductive system and breast disorders**

**Resp - Respiratory, thoracic and mediastinal disorders**

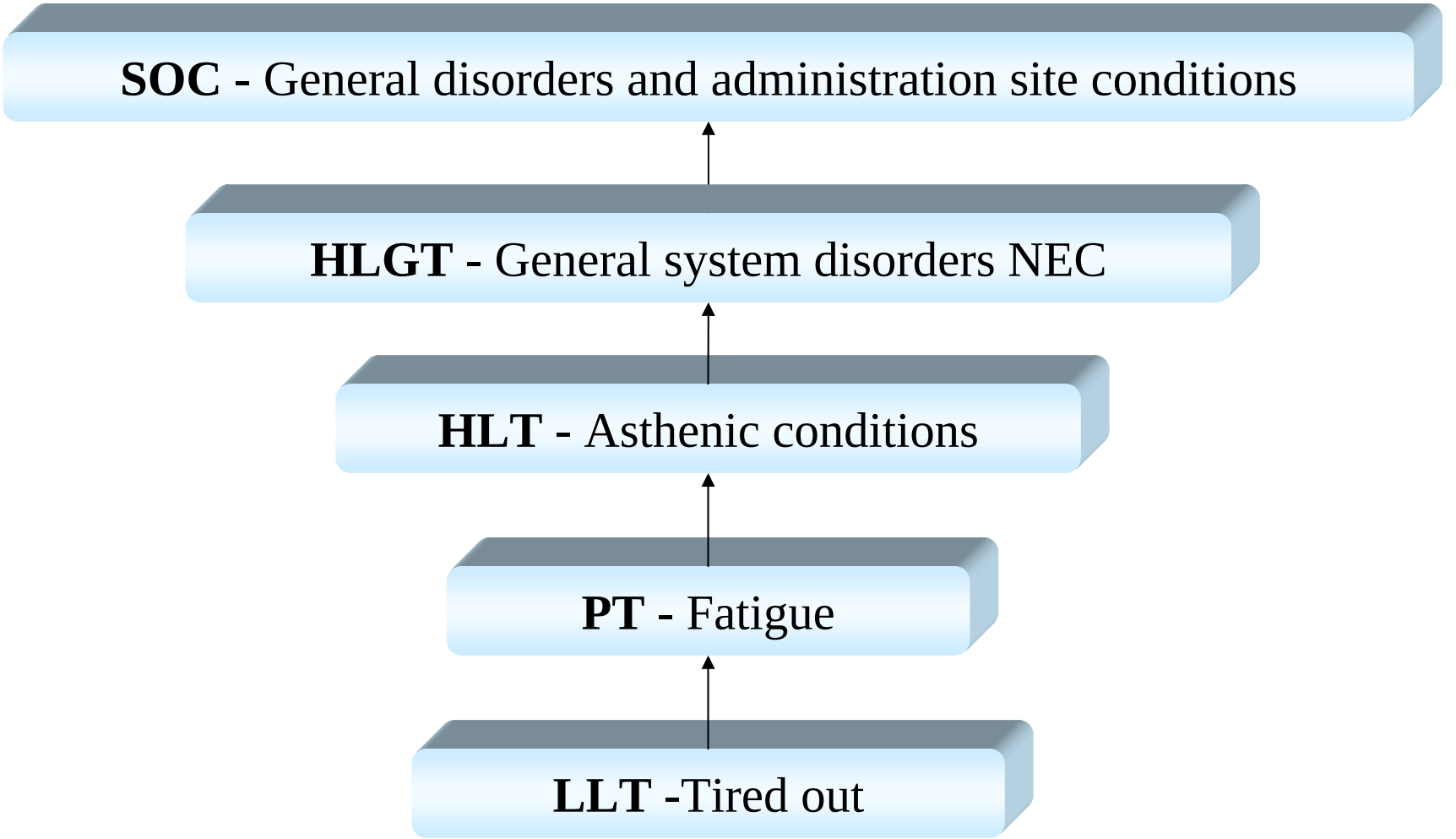
*Skin - Skin & subcutaneous tissue disorders*

**SocCi - Social circumstances**

**Surg - Surgical and medical procedures**

**Vasc - Vascular disorders**

# LLT to SOC


**SOC -** General disorders and administration site conditions
**HLGT -** General system disorders NEC
**HLT -** Asthenic conditions
**PT -** Fatigue
**LLT -**Tired out

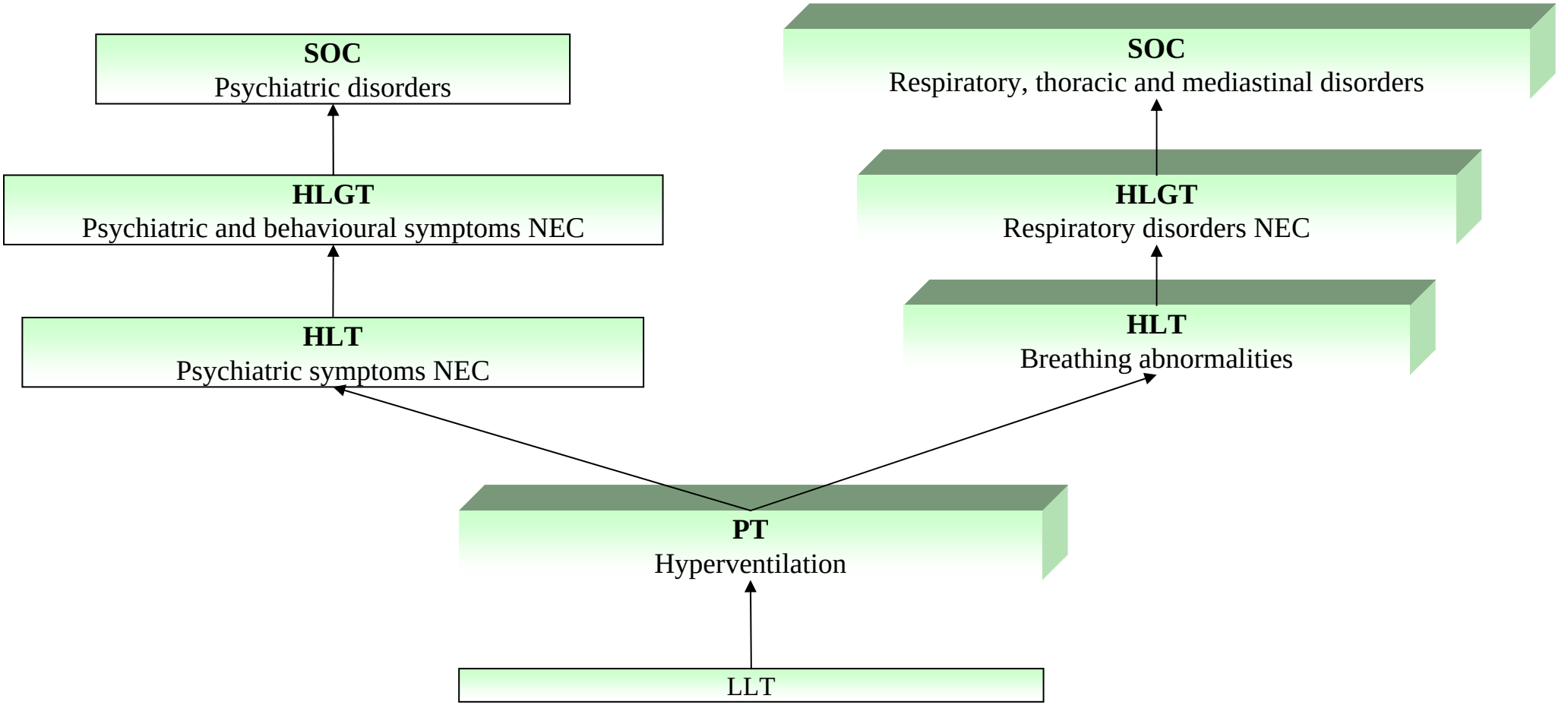
# Multiaxiality

- Terms can be represented in more than one hierarchical path
- Terms with more than one SOC will be assigned a primary SOC
- Allows different clinical retrievals for analysis and presentations
- Generally, PTs are assigned to the prime manifestation site system or organ-based SOC ***Example***:

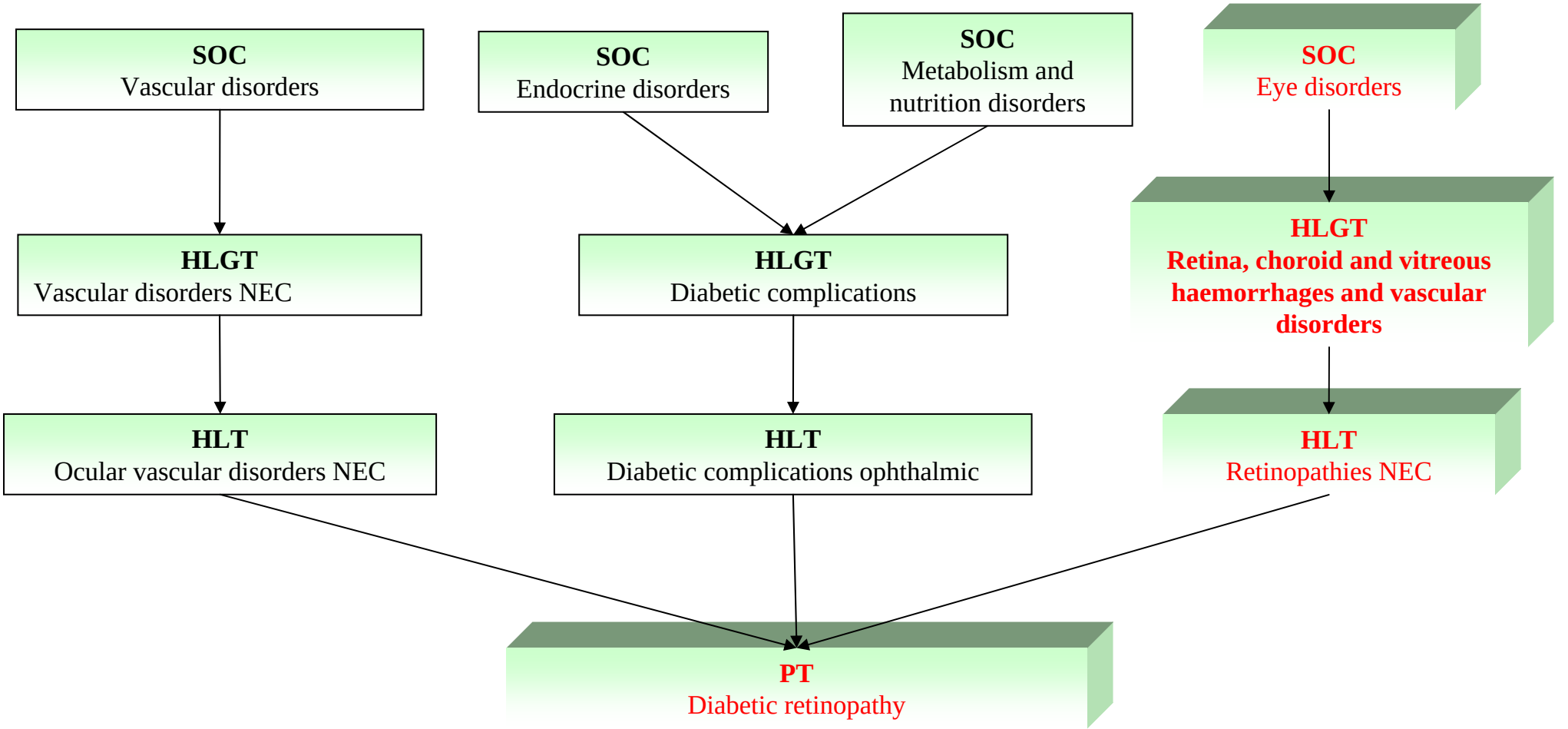
  PT “Cardiac failure”

  Primary SOC “Cardiac disorders”

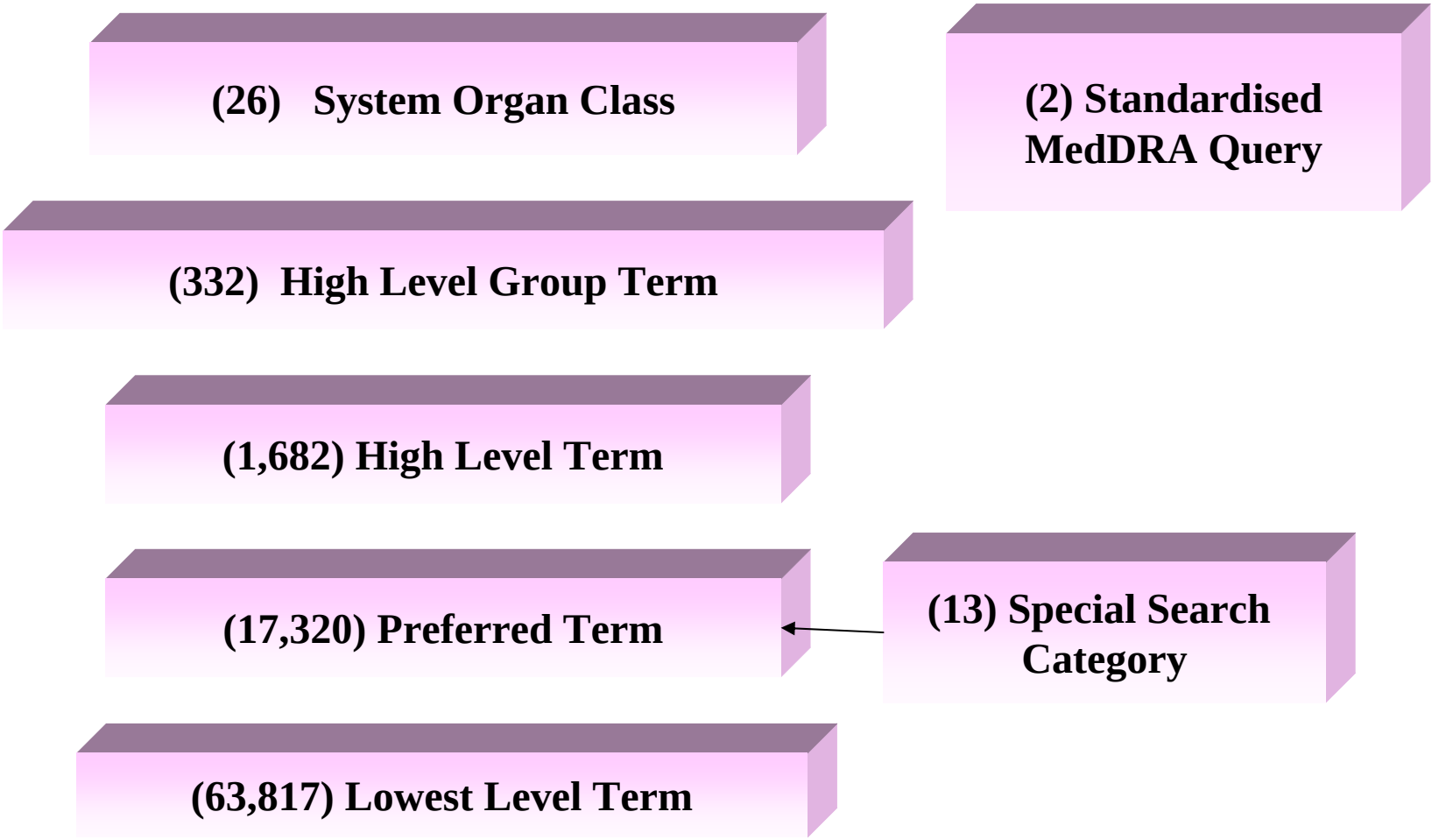
# Simple Multiaxial Mapping



# Complex Multiaxial Mapping



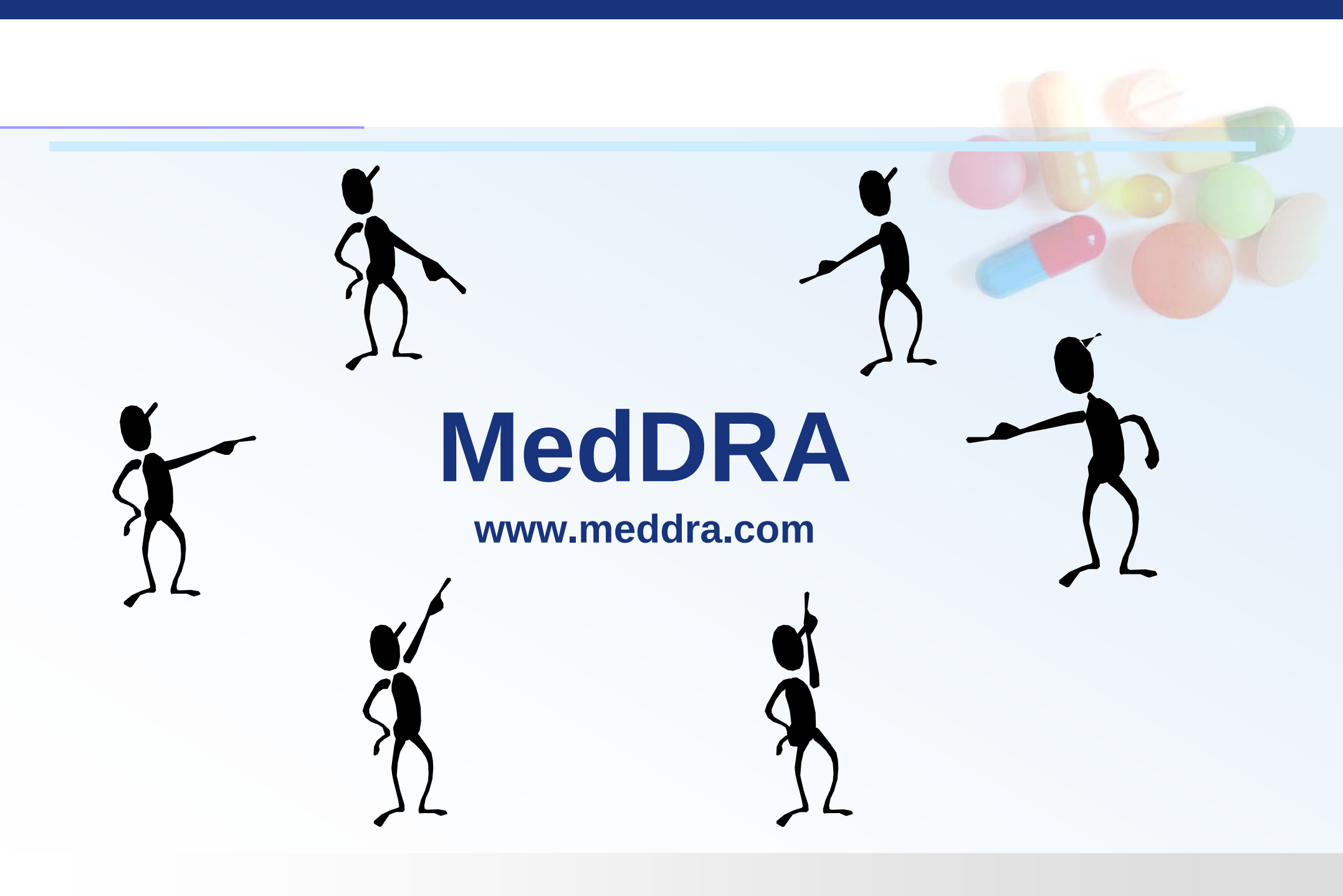
# Hierarchy (V9.0)



# What is new in MedDRA?

- New MedDRA versions are released in March and September each year.

- The Current version of MedDRA is version 14.0.


MedDRA
www.meddra.com

# Q & A ?

*Thanks for your attention ☺*