



# **A taxonomy for outcomes in medical research to help improve knowledge discovery**

Dr Susanna Dodd and Professor Paula Williamson  
MRC North West Hub for Trials Methodology Research  
University of Liverpool, UK

# Outcome classification

- Motivation:
  - Trial registries, Cochrane and COMET databases annotated studies according to “PIC” of PICO
    - Population
    - Intervention
    - Comparison
    - Outcomes: **were not classified/searchable**
  - Interest in outcome profiles across trials, COS and SRs
    - e.g. AEs, HRQL, survival

# Outcome classification structures

- Existing classification structures: **none fit for this purpose**
  - ICF (The International Classification of Functioning, Disability and Health, 2001)
  - Wilson & Cleary (1995)
  - PROMIS, NIH Toolbox (Neuro-behavioural)
  - DOMS (Dementia)
  - ASCQ-Me (Sickle Cell Anaemia)
  - Outcomes Measures Framework (OMF, Porter 2010) (e.g. applied to cancer, Carpenter 2012)
  - OMERACT (Rheumatology, Boers 2014)

# Classification of outcomes in SRs

- 99/299 COS included SR in COS development
- 72 did not classify outcomes
- 21 used their own classification method
- 6 used existing classification method
  - ICF to define context/content of categories (4)
  - Wilson & Cleary (1)
  - Roberts & Counsell (1)

Core domain	Smith et al	Cochrane	Williamson/Clarke	Dodd/Williamson/Clarke
Adverse events	1: AEs	1: AEs	1: AEs	1: AEs
Death	2: Mortality/survival	2: Mortality/survival	2: Mortality/survival	2: Mortality/survival
Physiological or clinical	3: Physiological/clinical	3: Physiological/clinical	3: Physiological/clinical	3-25: Physiological/clinical
	4: Infection	4: Infection	4: Infection	
	5: Pain	5: Pain	5: Pain	
Life Impact	6: ADLs	6: Function	6: ADLs	Functioning 26: Physical 27: Social 28: Role 29: Emotional/wellbeing 30: Cognitive
	7: Psychosocial	7: Psychosocial	7: Psychosocial	
		8: Mental Health	8: Mental Health	
	8: Quality of life	9: Quality of life	9: HRQL	
	9: Compliance	10: Compliance	10: Compliance	34: Delivery of care
	10: Withdrawal	11: Withdrawal/drop out		
	11: Satisfaction	12: Satisfaction with care	11: Satisfaction	
		13: Device/intervention failure		
Resource Use	12: Medication	14: Resource Use	12: Resource Use	Resource Use 35: Economic 36: Hospital 37: Need for further intervention 38: Societal/carers burden
	13: Economic			
	14: Hospital			
	15: Operative			

# Physiological/clinical domains

**Medical Dictionary for Regulatory Activities**

Summary Classes Properties Notes Mappings Widgets

Jump To:

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

Details Visualization N

Preferred Name

ID

cui

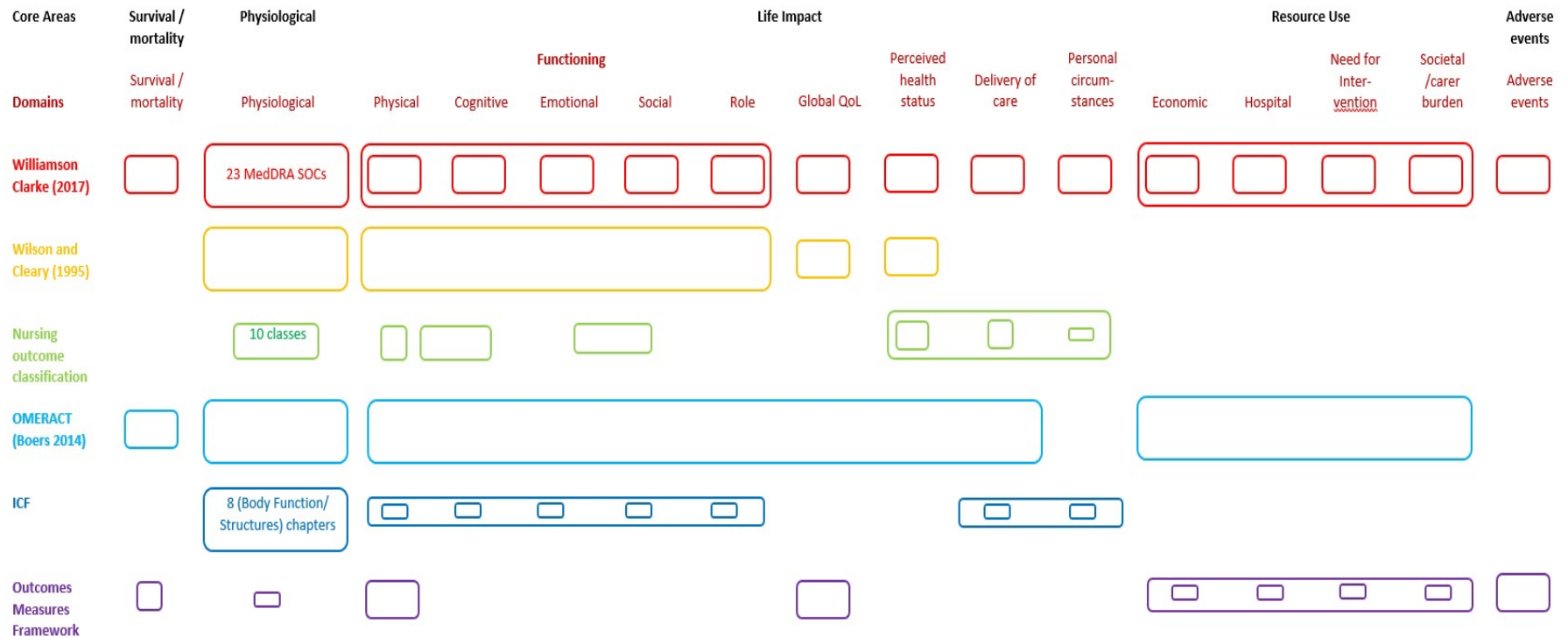
Inverse of SIB

- MedDRA (Medical Dictionary for Regulatory Activities)  
<http://www.meddra.org/>  
<http://bioportal.bioontology.org/ontologies/MEDDRA/?p=summary>
- System Organ Classes (highest level of classification) define our physiological/clinical domains
  - Excluding domains not relevant to physiology
    - Investigations
    - Product issues
    - Surgical and medicinal procedures
    - Social circumstances

# Physiological/clinical domains

- Blood and lymphatic system outcomes
- Cardiac outcomes
- Congenital, familial and genetic outcomes
- Endocrine outcomes
- Ear and labyrinth outcomes
- Eye outcomes
- Gastrointestinal outcomes
- General outcomes
- Hepatobiliary outcomes
- Immune system outcomes
- Infection and infestation outcomes
- Injury and poisoning outcomes
- Metabolism and nutrition outcomes
- Musculoskeletal and connective tissue outcomes
- Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)
- Nervous system outcomes
- Pregnancy, puerperium and perinatal outcomes
- Renal and urinary outcomes
- Reproductive system and breast outcomes
- Psychiatric outcomes
- Respiratory, thoracic and mediastinal outcomes
- Skin and subcutaneous tissue outcomes
- Vascular outcomes

# Outcome taxonomies





# Testing and validation

- COMET database of COS studies
  - Outcomes from 299 COS published up till 2015
- Cochrane Linked Data Project
  - 3515 Cochrane reviews from “Pregnancy and Childbirth” and “Neonatal” groups
  - 16525 outcome classifications
- Trial registry entries
  - <https://clinicaltrials.gov>
  - 30 phase III or IV interventional studies currently recruiting registered in January 2017
  - Case studies linking to specific COS:
    - Eczema (8 trials)
    - Rheumatoid arthritis (10 trials)

# COS outcomes (not involving patients)

Domain	n (% of 234)	Domain	n (% of 234)
<b>Mortality/survival</b>	82 (35)	Perceived health status	0 (0)
<b>Physiological/clinical (≥1)</b>	213 (91)	Delivery of care	43 (18)
Functioning (≥1)	84 (36)	Personal circumstances	0 (0)
Physical	70 (30)	<b>Resource use (≥1)</b>	67 (29)
Social	14 (6)	Economic	33 (14)
Role	10 (4)	Hospital	16 (7)
Emotional/wellbeing	19 (8)	Need for intervention	34 (15)
Cognitive	13 (6)	Societal/carer burden	3 (1)
Global quality of life	90 (38)	<b>Adverse events/effects</b>	82 (35)
<b>Global quality of life/Functioning (≥1)</b>	<b>126 (54)</b>		

# COS outcomes (involving patients)

Domain	n (% of 65)	Domain	n (% of 65)
<b>Mortality/survival</b>	17 (26)	Perceived health status	0 (0)
<b>Physiological/clinical (≥1)</b>	61 (94)	Delivery of care	10 (15)
Functioning (≥1)	44 (68)	Personal circumstances	0 (0)
Physical	41 (63)	<b>Resource use (≥1)</b>	17 (26)
Social	11 (17)	Economic	4 (6)
Role	1 (2)	Hospital	8 (12)
Emotional/wellbeing	10 (15)	Need for intervention	11 (17)
Cognitive	8 (12)	Societal/carer burden	2 (3)
Global quality of life	31 (48)	<b>Adverse events/effects</b>	23 (35)
<b>Global quality of life/Functioning (≥1)</b>	<b>51 (78)</b>		

# Cochrane Linked Data Project

	Number (%) of 3515 Cochrane reviews	Number (%) of 16525 outcome classifications
Adverse events	596 (17)	951 (6)
Mortality	857 (24)	1246 (8)
Physiological	2915 (83)	9820 (59)
Function/QoL	831 (24)	1844 (11)
Delivery of care	419 (12)	493 (3)
Resource use	1117 (32)	2171 (13)

# COS uptake: Rheumatoid arthritis

Outcome domain	Core outcomes	Number (% of 10 trials)
Musculoskeletal	Tender joints	8 (80%)
Musculoskeletal	Swollen joints	8 (80%)
Musculoskeletal	Pain	5 (50%)
General (physiological)	Physician global assessment	6 (60%)
General (physiological)	Patient global assessment	6 (60%)
Physical functioning	Physical disability	6 (60%)
Musculoskeletal	Acute phase reactants	6 (60%)

# COS uptake: Eczema

Outcome domain	Core outcomes	Number (% of 8 trials)
Skin (physiological)	Clinician-reported signs	3 (37.5%)
Skin (physiological)	Patient-reported symptoms	0 (0%)
Function/Global QoL	Quality of life	3 (37.5%)
Skin (physiological)	Long-term control of flares	2 (25%)

# Composite outcomes

- Outcomes which cover multiple domains should be classified in **all** relevant domains
  - e.g. Composite survival outcomes
    - Disease-free survival would be classified under relevant physiological domain AND *Mortality/survival*
    - Amputation-free survival would be classified under *Need for further intervention* AND *Mortality/survival*
  - “Treatment failure due to inefficacy or side effects”
    - Categorise within the relevant physiological domain, AE domain and *Delivery of care*

# AE domain: two-level categorisation

- Adverse events/effects domain
  - Only includes outcomes explicitly labelled as some form of unintended consequence of the intervention
    - e.g. safety, harm, negative effects, adverse effects/events/drug reactions, toxicity, complications, sequelae
  - Not intended to include specifically named AEs
- Specifically named AEs
  - Categorise within relevant taxonomy domain, with secondary component to identify adverse (rather than benefit) outcome
  - i.e. Two-level taxonomy
    - First-level: outcome domain
    - Second-level: adverse/benefit outcome



# AE domain: two-level categorisation

- Death is not necessarily classified as an AE
  - e.g. If aim of surgery is to improve length of survival, then “death” would be a benefit outcome
  - However, death related to intervention would be a harm outcome, e.g. “treatment-related death”
    - Classify under *Mortality/survival*
    - Secondary component identifies it as an adverse outcome

# AE domain: broad-level complications

- AE domain is relevant for broad-level complications related to the **intervention**
  - e.g. Anaesthetic complications
  - e.g. Operative morbidity
- AE domain is **not** relevant for broad-level complications linked to a **condition**
  - Classify within the relevant physiological domain with second component identifying it as a harm outcome
  - e.g. Bowel-related complications would be classified as a harm outcome within *Gastrointestinal* domain

# General and specific AEs

- When specific AEs are listed as examples of a general AE outcome
  - Each **specifically named** AE should be classified within the appropriate domain (with the second component identifying it as a harm outcome)
  - The **general term** should be classified within *AE* domain
  - e.g. “Adverse events (e.g. pain, fatigue, hospitalisation)”
    - Pain, fatigue – *General* outcomes domain (identified as harms)
    - Hospitalisation – *Hospital* domain (identified as harm)
    - Adverse events – *AE* domain

# Quality of life

- “Health Related Quality of Life” (HRQL)
  - Commonly reported without further detail
  - HRQL tools may measure features/outcomes relevant to domains other than just *Global quality of life*
    - For example, facets within WHOQOL-100 domain cover
      - *Global QoL*
      - *Functioning domains (all)*
      - *Personal circumstances*
      - *Societal/carer burden*
      - *Delivery of care*
  - Categorise summary measures in **all** relevant domains
    - Recommend that HRQL tools should be split into individual components, rather than just summarising an overall score (as per Macefield 2014)

WHOQOL-100 domain	Facet within WHOQOL-100 domain	Outcome taxonomy domain
	Overall QoL and General Health	Global quality of life
Physical health		
	Energy and fatigue	Physical functioning
	Pain and discomfort	Physical functioning
	Sleep and rest	Physical functioning
Psychological		
	Bodily image and appearance	Emotional functioning (emotions)
	Negative feelings	Emotional functioning
	Positive feelings	Emotional functioning
	Self-esteem	Emotional functioning
	Thinking, learning, memory and concentration	Cognitive functioning
Level of independence		
	Mobility	Physical functioning
	Activities of daily living	Physical functioning
	Dependence on medicinal substances and medical aids	Need for further intervention
	Work capacity	Role functioning

WHOQOL-100 domain	Facet within WHOQOL-100 domain	Outcome taxonomy domain
<b>Social relationships</b>		
	Personal relationships	Social functioning
	Social support	Societal/carer burden
	Sexual activity	Social functioning
<b>Environment</b>		
	Financial resources	Personal circumstances
	Freedom, physical safety and security	Emotional functioning (feelings); Personal circumstances (environment)
	Health and social care; accessibility and quality	Delivery of care
	Opportunities for acquiring new information and skills	Personal circumstances
	Participation in and opportunities for recreation/leisure activities	Social functioning (participation); Personal circumstances (opportunities)
	Physical environment (pollution/noise/traffic/climate)	Personal circumstances
	Transport	Personal circumstances
<b>Spirituality/Religion /Personal beliefs</b>		
	Spirituality/Religion/Personal beliefs	Cognitive functioning

# Physiological outcomes

- Categorised according to the underlying cause or affected body system
- *General* outcomes
  - Those affecting the whole body which cannot be attributed to a certain body system, for example:
    - Fatigue, chills, flu like symptoms, malaise, anorexia
    - Pain (unspecified), fever (not attributable to infection)
    - Anthropometric measures (e.g. weight)
    - “Symptoms” (not associated with particular body system)
    - “Global” measures, “physical health”, fitness

# Physiological outcomes

- Laboratory/scientific measures
  - Classify within the physiological domain that captures the **reason** for the assessment
  - e.g. Pharmacokinetic outcomes
  - e.g. Blood samples
    - HbA1c in diabetes trial: *Endocrine* domain
- Bleeding events
  - Classify within *Vascular* domain (rather than *Injury* or *Blood and lymphatic system*)



# Physiological or impact?

- For example, sleep outcomes
  - Clinical signs, symptoms, lab measures: classify within relevant physiological domain
    - *Nervous system, Psychiatric OR Metabolism and nutrition*
    - Use guidance from MedDRA and clinical knowledge
  - Categorise within functioning domains if explicitly focused on impact on the patient's life
    - “Impact of sleep deprivation on ability to work”  
*Role functioning*
    - “Inability to concentrate due to sleep deprivation”  
*Cognitive functioning*

# Physiological or impact?

- Ambiguous?
  - For example, sleep quality/duration
    - Physiological measures
      - Number of hours sleep, Number of sleep disturbances
    - Does this imply impact?
      - Able to sleep well, Getting enough deep sleep
  - When in doubt, classify in **all** potentially relevant domains

# Delivery of care

- Variables related to health care intervention
  - Compliance, withdrawal from intervention
    - e.g. “Time to treatment failure”
  - Patient preference, patient or carer satisfaction
  - Appropriateness, accessibility, quality and adequacy of intervention
  - Process, implementation and service outcomes
  - Technical aspects of surgery
    - e.g. “Conversion to open surgery”

# How, what, who...?

- The taxonomy is intended for classification of **what**, rather than **how**, outcomes are measured
  - How: [www.cosmin.nl](http://www.cosmin.nl)
- Classification does NOT depend on **who** (e.g. clinician versus patient) is recording outcome
  - e.g. Patient-reported measure of “response to treatment” would still be classified as a physiological outcome, unless defined specifically in terms of impacting patient’s life

# Future development

- Taxonomy explanation table and user guidance on COMET website
  - <http://www.comet-initiative.org/OutcomeClassification>
  - **Regular updates** to include further clarification based on feedback or queries received
  - Users are invited to deposit their outcome classifications and/or classifications for HRQL tools to aid other researchers
    - <http://www.comet-initiative.org/OutcomeClassification/Deposit>
- Further subdivision of high-level domains by researchers specialising in relevant clinical or methodological areas
  - e.g. DSM could be used to classify mental disorders within the psychiatry domain
- We welcome feedback from users!



**Core Outcome Measures in Effectiveness Trials**

**[www.comet-initiative.org](http://www.comet-initiative.org)**

Twitter: @COMETinitiative