Outcome Taxonomy User Guide

A taxonomy suitable for classification of outcomes included in trials, core outcome sets (COS), systematic reviews (SRs) and trial registries has been developed (see supplementary table 1 in Dodd 2018, https://doi.org/10.1016/j.jclinepi.2017.12.020).

This user guide provides explanations and examples of how outcomes should be classified using this taxonomy (see also http://www.comet-initiative.org/OutcomeClassification/).

Please note the following important points:

1. The taxonomy is intended for the classification of what, rather than how, outcomes are measured.
2. The taxonomy relates to outcomes measured at an individual-patient level (including those relating to the direct impact of the individual patient's treatment or condition on wider society, for example resource use or carer burden) but is not intended to cover outcomes relating to the health or functioning of wider society (for example, family or community health). Therefore, health promotion or public health outcomes from trials of family- or community-based interventions can be classified using our taxonomy if they relate to an individual's condition or care, but not if they are measured at the family or community level.
3. The authors of this taxonomy are not suggesting that trials, COS or SRs should necessarily include outcomes from each of the core areas in this taxonomy.
4. Classifications of outcomes using this taxonomy are intended to comprise two components, the first defining the outcome structure (as defined in the 38-item scale described in the table referenced above) and the second specifying whether the outcome is being measured as a benefit (intended improvement in health or wellbeing) or a harm (unintended consequence of the intervention under study) outcome.
5. Outcomes which cover multiple domains (for example, composite outcomes) should be classified in all relevant domains.
6. We are confident that our taxonomy provides a sufficiently comprehensive basis for the categorisation of outcomes included in clinical trials in general, and hope that this taxonomy will assist COS developers who need to categorise outcomes, for example as part of their Delphi survey, or systematic reviewers who wish to annotate their review outcomes according to outcome type. However, we would welcome feedback from researchers applying the taxonomy in their clinical settings in order to demonstrate further validation of the taxonomy or to highlight any necessary changes.
7. Explanations and examples of outcomes within each outcome domain are given in Table 3 below. We will monitor use of the taxonomy and collate feedback and common queries, and the explanation table will be regularly updated to address ambiguities and answer frequently asked questions.
8. Note that outcome descriptions in trials, COS and SRs are not always sufficiently detailed to facilitate confident classification. Researchers are encouraged to give as much detail as possible when defining outcomes in order to aid classification.

Adverse event outcomes

1. Any specifically named adverse events (AEs) (for example, fatigue or pain) should be categorised under the appropriate taxonomy domain, rather than within the adverse event domain, with the second component identifying the outcome as a harm (rather than benefit) outcome.
    - For example, the COS for colorectal cancer surgery (ref McNair) includes faecal urgency, which is a potential adverse effect of the surgery. This would be classified as a physiological outcome, under the gastrointestinal category, but the second component would identify it as an adverse outcome.
    - Note that death is not necessarily classified as an AE. For example, if the purpose of surgery is to improve length of survival, then "death" would be a benefit outcome. However, death related to intervention (e.g. "treatment-related death") would be a harm outcome and should therefore be classified under "mortality/survival" with a secondary component identifying it as an adverse outcome.
2. In contrast, the AE domain only includes outcomes explicitly labelled as some form of unintended consequence of the intervention, such as "adverse events", "adverse effects", "adverse reactions", "complications", "toxicity" or "sequelae".
3. If specific AEs are listed as examples of a general AE outcome, such as "Adverse events (e.g. pain, fatigue, hospitalisation)", then each specifically named AE should be classified within the appropriate domain (with the second component identifying it as a harm outcome) but the general term ("Adverse events") should also be classified within the AE domain.
4. This AE domain is also relevant for broad-level complications related to the intervention (e.g. "Anaesthetic Complications" or "Operative morbidity"). However broad-level complications linked to a condition (e.g. "Bowel-related complications") should be classified within the relevant physiological domain (e.g. "Gastrointestinal"), with the second component identifying it as a harm outcome.
5. The AE domain, which is not intended to include any specifically named adverse events, is important as it indicates whether or not trialists or researchers considered the need to record events that may not necessarily be prespecified ahead of time.

Physiological/clinical outcomes

Physiological outcomes are categorised according to the underlying cause or affected body system, grouped using the MedDRA System Organ Classes (SOCs). Users are advised to search the MedDRA categories listed within Bioportal to identify the relevant domain within which to classify outcomes (see http://bioportal.bioontology.org/ontologies/MEDDRA/?p=classes&conceptid=root). For example,

1. "Endocrine outcomes" are those associated with endocrine disorders.
2. Sleep outcomes may be classified as "nervous system outcomes", "psychiatric outcomes" or "metabolism and nutrition disorders", depending on cause.
3. "Outcomes related to neoplasms" include those relating to physiological function, signs and symptoms caused by benign, malignant and unspecified (including cysts and polyps) neoplasms, including solid and non-solid tumours. Examples of such outcomes include "time to recurrence", "response rate" and "clearance of resection margins".
4. "General outcomes" include 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, not associated with a particular body system), fever (not attributable to infection), anthropometric measures (e.g. weight), "global" measures, "symptoms" (not associated with a particular body system), "physical health" and fitness.
5. Laboratory parameters (for example, from blood samples) and scientific measures (for example, pharmacokinetic outcomes) should be classified within the physiological domain that captures the reason for the assessment (rather than within the "blood and lymphatic system" category, for example). For example, if HbA1c was measured in a diabetes trial, it would be classified within the "endocrine" physiological domain.
6. "Injury" outcomes such as "gastrointestinal injury" should be classified under the appropriate physiological/clinical domain ("gastrointestinal") rather than within the "injury/poisoning" domain – and recorded as an adverse event.
7. Bleeding events should be classified as "vascular" outcomes, rather than "injury" or "blood and lymphatic system".

Physiological or impact?

1. Anthropometric outcomes, such as body weight, should be classified as "general outcomes" rather than "metabolism/nutrition outcomes". However, outcomes relating to weight may instead/also be a measure of impact (i.e. relating to one or more of the functioning domains). Further information may be required (e.g. in terms of the measurement tool/exact wording of the questions) to determine whether the outcome is relating to the physiological symptom or the impact of that symptom. For example, outcomes such as "diarrhoea" and "malabsorption" may relate to both/either "gastrointestinal" and "physical functioning", depending on context.
2. Outcomes such as sleep may also be classified as either physiological or functioning, depending on focus. For example, outcomes relating to the impact of sleep deprivation would be classified within the relevant functioning domain:
    a. "Physical exhaustion due to sleep deprivation" would be classified within "physical functioning".
    b. "Impact of sleep deprivation on ability to work" would be classified within "role functioning".
    c. "Impact of sleep deprivation on ability to socialise" would be classified within "social functioning".
    d. "Inability to cope due to sleep deprivation" would be classified within "emotional functioning".
    e. "Inability to concentrate due to sleep deprivation" would be classified within "cognitive functioning".

    In contrast (and probably more commonly), sleep outcomes which relate to clinical signs, symptoms, lab measures, etc. would be classified under the relevant physiological domain, according to the MedDRA hierarchy. We would therefore recommend that researchers use a combination of their clinical knowledge and guidance by MedDRA to classify physiological sleep outcomes into the appropriate domain.
3. When in doubt, we would recommend classifying outcomes in all potentially relevant domains (e.g. functioning and/or any of the potentially relevant physiological domains).
4. Note that the classification of outcomes does not depend on who (e.g. clinician versus patient) is recording the outcome: for example, a patient-reported measure of "response to treatment" would still be considered a physiological/clinical outcome, unless it was defined specifically in terms of impacting the patient's life.

Delivery of care outcomes

1. The "delivery of care" domain contains variables related to health care interventions, including compliance, withdrawal and satisfaction. These variables are grouped within the same domain as they are all related to the appropriateness and acceptability of the intervention and may not be easily distinguishable (for example because of overlap between issues relating to compliance, satisfaction with care, withdrawal, treatment failure).
2. Examples of outcomes in this category include patient preference; withdrawal from intervention (e.g. time to treatment failure); appropriateness, accessibility, quality and adequacy of intervention; patient or carer satisfaction; and process, implementation and service outcomes.
3. Technical aspects of surgery should be classified within the "delivery of care" domain, as they relate to the delivery of intervention. Outcomes such as "conversion to open surgery" indicate failure of intervention, which is included within this domain.

Health related quality of life measurement tools

1. Health related quality of life (HRQL) measurement tools typically cover multiple domains (such as functioning, resource use, general physiological health and global quality of life) and should therefore be classified within each of these separate domains, even when overall summary measures are reported, as we would recommend for any composite outcome.
2. The "global quality of life" domain in our taxonomy is reserved for specific individual questions or tools which measure the implicit composite outcome of global quality of life (for example, "How would you rate your overall quality of life?"), rather than for overall summary measures from HRQL tools covering multiple domains.
3. Researchers are invited to submit their domain classifications for HRQL measurement tools (see http://www.comet-initiative.org/OutcomeClassification/Deposit).

Composite outcomes

1. Outcomes which cover multiple domains (e.g. if the questions included in a HRQL measurement tool relate to more than one domain) should be classified in all relevant domains.
2. Similarly, composite survival outcomes (e.g. disease-free survival) need to be classified according to the condition/disease as well as under "mortality/survival". Amputation-free survival would be classified under "need for further intervention" and "mortality/survival".
3. "Time to treatment failure" may be defined as specifically including events relating to relapse, progression, death, etc. In this case, this outcome should be classified within the "delivery of care" domain and all other domains relating to the included event types (for example, "treatment failure due to inefficacy or side effects" would be categorised within the relevant physiological domain and AE domain, as well as the "delivery of care" domain).

Deposit your outcome classifications

We welcome feedback from researchers who have applied the taxonomy to outcomes in their SR, Delphi study or final COS. We will happily respond to queries and check outcome classifications, and you are invited to submit your lists of outcomes and associated taxonomy classifications for inclusion in our repository (http://www.comet-initiative.org/OutcomeClassification/Deposit). You are requested to download and populate an Excel spreadsheet (see Table 1 below) providing the title and authors of your COS/SR, indication of the source of the outcome list (SR, Delphi study, final COS, other – please specify), verbatim outcome text and associated taxonomy domain for each outcome, and any comments or queries you may have. We also welcome submissions of outcome classifications associated with HRQL measurement tools (see Table 2 below).

Table 1 Excel spreadsheet 1: Outcome taxonomy classifications

COS/SR title:		
Authors:		
COMET database entry URL or publication reference:		
Outcome list relates to:	Systematic review of clinical research studies	
	Interviews/focus groups with patients	
	Delphi study	
	Final core outcome set	
	Other (please specify)	
Outcome (verbatim text)	**Taxonomy domain**	**Comment/query**

Table 2 Excel spreadsheet 2: HRQL measurement tool taxonomy classifications

COS/SR title:		
Authors:		
HRQL measurement tool (with URL or publication reference):		
Outcome/questions in tool	**Taxonomy domain**	**Comment/query**

References

Dodd SR, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. (2018) A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. Journal of Clinical Epidemiology, 96:84-92

McNair, A.G.K., Whistance, R.N., Forsythe, R.O., Macefield, R., Rees, J., Pullyblank, A.M. et al. Core outcomes for colorectal cancer surgery: a consensus study. PLoS Med. 2016; 13: e1002071

Table 3 Taxonomy explanation and examples table

Core area	Outcome domain	Explanation
Death	1. Mortality/survival	Includes overall (all-cause) survival/mortality and cause-specific survival/mortality, as well as composite survival outcomes that include death (e.g. disease-free survival, progression-free survival, amputation-free survival)
Physiological/ clinical	**Physiological/clinical** 2. Blood and lymphatic system outcomes 3. Cardiac outcomes 4. Congenital, familial and genetic outcomes 5. Endocrine outcomes 6. Ear and labyrinth outcomes 7. Eye outcomes 8. Gastrointestinal outcomes 9. General outcomes 10. Hepatobiliary outcomes 11. Immune system outcomes 12. Infection and infestation outcomes 13. Injury and poisoning outcomes 14. Metabolism and nutrition outcomes 15. Musculoskeletal and connective tissue outcomes 16. Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps) 17. Nervous system outcomes 18. Pregnancy, puerperium and perinatal outcomes 19. Renal and urinary outcomes 20. Reproductive system and breast outcomes 21. Psychiatric outcomes	Physiological/clinical outcomes include measures of physiological function, signs and symptoms, as well as laboratory (and other scientific) measures relating to physiology, and are categorised according to the underlying cause/body system. "General disorders" includes those affecting the whole body and cannot be attributed to a certain body system e.g. fatigue, chills, flu like symptoms, malaise, anorexia, pain (unspecified, not associated with a particular body system), fever (not attributable to infection), anthropometric measures (e.g. weight), "global" measures, "symptoms" (not associated with a particular body system), "physical health", fitness. Pain outcomes are categorised according to underlying cause or body system or within the "General symptoms" category (if non-specific). Laboratory parameters (for example, from blood samples) and scientific measures (for example, pharmacokinetic outcomes) should be classified within the physiological domain that captures the reason for the assessment (rather than within the "blood and lymphatic system" category, for example). Psychiatric outcomes include all those relating to mental health conditions and associated behaviours (e.g. addictions and behavioural problems). Pregnancy, puerperium and perinatal domain extends to outcomes relating to breastfeeding and weaning. Outcomes relating to neoplasms include those related to non-solid and solid tumours.

Core area	Outcome domain	Explanation
	22. Respiratory, thoracic and mediastinal outcomes 23. Skin and subcutaneous tissue outcomes 24. Vascular outcomes	
Life impact	**Functioning** 25. Physical functioning 26. Social functioning 27. Role functioning 28. Emotional functioning/wellbeing 29. Cognitive functioning	**Impact outcomes** Physical functioning: impact of disease/condition on physical activities of daily living (for example, ability to walk, independence, self-care, performance status, disability index, motor skills, sexual dysfunction. health behaviour and management) Social functioning: impact of disease/condition on social functioning (e.g. ability to socialise, behaviour within society, communication, companionship, psychosocial development, aggression, recidivism, participation) Role functioning: impact of disease/condition on role (e.g. ability to care for children, work status) Emotional functioning/wellbeing: impact of disease/condition on emotions or overall wellbeing (e.g. ability to cope, worry, frustration, confidence, perceptions regarding body image and appearance, psychological status, stigma, life satisfaction, meaning and purpose, positive affect, self-esteem, self-perception and self-efficacy) Cognitive functioning: impact of disease/condition on cognitive function (e.g. memory lapse, lack of concentration, attention); outcomes relating to knowledge, attitudes and beliefs (e.g. learning and applying knowledge, spiritual beliefs, health beliefs/knowledge)
	30. Global quality of life	Includes only implicit composite outcomes measuring global quality of life
	31. Perceived health status	Subjective ratings by the affected individual of their relative level of health

Core area	Outcome domain	Explanation
	32. Delivery of care	Includes outcomes relating to the delivery of care, including • adherence/compliance • patient preference • tolerability/acceptability of intervention • withdrawal from intervention (e.g. time to treatment failure) • appropriateness of intervention • accessibility, quality and adequacy of intervention • patient/carer satisfaction (emotional rather than financial burden) • process, implementation and service outcomes (e.g. overall health system performance and the impact of service provision on the users of services)
	33. Personal circumstances	Outcomes relating to patient's finances, home and environment
Resource use	**Resource use** 34. Economic 35. Hospital 36. Need for further intervention 37. Societal/carer burden	Economic: general outcomes (e.g. cost, resource use) not captured within other specific resource use domains Hospital: outcomes relating to inpatient or day case hospital care (e.g. duration of hospital stay, admission to ICU) Need for further intervention: outcomes relating to medication (e.g. concomitant medications, pain relief), surgery (e.g. caesarean delivery, time to transplantation) and other procedures (e.g. dialysis-free survival, mode of delivery) Societal/carer burden: outcomes relating to financial or time implications on carer or society as a whole (e.g. need for home help, entry to institutional care, effect on family income)
Adverse events	38. Adverse events/effects	Includes outcomes broadly labelled as some form of unintended consequence of the intervention (e.g. adverse events/effects, adverse reactions, safety, harm, negative effects, toxicity, complications, sequelae). Specifically named adverse events should be classified within the appropriate taxonomy domain above with an additional level of categorisation which identifies that this outcome is being considered as an adverse event.

Linking Cochrane version with published version of taxonomy

The table below shows how the published version of the taxonomy links with the version adopted by Cochrane. Domains in the same row of the table link directly between the two versions of the taxonomy, except where footnotes indicate that other domains may also be relevant.

Core area	Cochrane version	Published version
Adverse events	Adverse events	Adverse events
Death	Mortality/survival	Mortality/survival
Physiological or clinical	Physiological/clinical	23 Physiological/clinical domains (MedDRA System Organ Classes)
	Infection[1]	
	Pain[2]	
Life impact	Function[3]	Physical functioning
		Role functioning
		Cognitive functioning
	Mental health[4]	Emotional/wellbeing functioning
	Psychosocial[5]	Social functioning
	Quality of life	Global quality of life
		Perceived health status
		Personal circumstances
	Compliance	Delivery of care
	Withdrawal/drop out	
	Satisfaction with care	
	Device/intervention failure	
Resource use	Economic	Economic
	Medication	Need for further intervention[6]
	Operative	
	Hospital	Hospital
		Societal/carer burden

[1] Infection outcomes fall within the "Infection and infestation" physiological domain.

[2] Pain outcomes are categorised in the relevant physiological (MedDRA SOC) domain according to underlying cause or body system or within the "General symptoms" domain (if non-specific).

[3] Function outcomes may extend beyond "Physical functioning" to any of the other functioning domains (e.g. "Role functioning" or "Cognitive functioning").

[4] Mental health outcomes which assess physiological or clinical measures should instead be classified within the "Psychiatric" domain of the Physiological/clinical area.

[5] Psychosocial outcomes may also relate to "Emotional/wellbeing functioning" as well as "Social functioning".

[6] Note that "Need for further intervention" includes non-surgical procedures (such as dialysis and mode of childbirth delivery) which are not covered by the "Medication" or "Operative" domains within the Cochrane version of the taxonomy.