Concept Paper

Principles for Simplification of Biopharmaceutical Product Safety Labeling by Grouping Similar MedDRA® Terms for Unique Medical Concepts

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Executive Summary

An Expert Working Group (EWG) coordinated by the Council for International Organizations of Medical Sciences (CIOMS) is proposed to develop principles and pragmatic recommendations to promote consistency and understandability of medical concepts, e.g. suspected adverse reactions (SARs), in biopharmaceutical product safety labeling. The granularity and structure of Medical Dictionary for Regulatory Activities (MedDRA) provide opportunities for precision in coding verbatim safety terms to MedDRA terms. However, the high granularity of MedDRA could obscure medical concepts that are labeled SARs and, thus, are important to communicate to healthcare providers. The established MedDRA hierarchy provides groupings of related and meaningful medical concepts but these groupings are often inadequate to clearly communicate unique clinical concepts that are coded as different, but similar, MedDRA terms. To simplify communication of such concepts that are not supported by the existing MedDRA hierarchy, the proposed CIOMS EWG would develop principles and points to consider for development of MedDRA Labeling Groupings (MLGs) that are needed but not currently represented in the published MedDRA terminology. Examples where the MLG concept could be applied to supplement the existing hierarchy are in Reference Safety Information (RSI), such as medical product prescribing information, Investigator Brochures, or other aggregate safety data presentations.

Driven by business needs and regulatory guidance, many organizations, e.g., sponsors, applicants, and regulators, have already begun to independently develop institution-specific approaches to clustering similar terms for RSI on a product-by-product basis. However, there are no agreed conventions or specific considerations that describe which terms may be appropriate to group together. The proposal in this Concept Paper addresses the urgent need to harmonise an international approach to creating and using MLGs in RSI. It is envisaged that use of the EWG's consensus MLG considerations would be voluntary, i.e., non-binding for regulatory compliance purposes, and would be applied to RSI only when appropriate.

Type of Harmonization Action Proposed

Harmonization of the approach to grouping terms for RSI is proposed. This harmonization action is important because there are no agreed conventions or considerations that describe consensus principles for grouping terms in situations when the MedDRA hierarchy is inadequate to describe selectively and completely clinically related concepts in RSI. Such a consensus approach would be used when appropriate term groupings are not available in the existing MedDRA hierarchy.

In certain instances, however, the published MedDRA hierarchy has grouped terms that can be included in RSI without modification. For example, High Level Term (HLT) *Renal lithiasis* (10038478)[1], represents a grouping of Preferred Terms (PTs) at a higher level of MedDRA that may be suitable for direct representation in RSI. In most instances, however, HLTs are too broad to describe a specific unique medical concept in RSI (see Appendix II, III). Also, the level of detail intrinsic to MedDRA, a regulatory terminology, may not always be easily understood by the healthcare community in meaningful ways, i.e., communication of important safety concepts to prescribers may be obscured.

While specific consensus recommendations on MLG principles would be made by the proposed EWG, there are several examples in the Appendix II, III that underscore the need for such principles. Note that the proposed EWG would not actually create MLGs, i.e., would not create another aspect of the MedDRA structure, but, rather, would **propose consensus principles for MLG creation and application**. Engagement of CIOMS in this effort is logical because of the ongoing involvement of the CIOMS Implementation Working Group (IWG) on Standardized MedDRA Queries (SMQs). The CIOMS SMQ IWG has an established process for navigating the MedDRA hierarchy and tested experience in grouping terms to retrieve adverse events of interest. This is often manifested in a collection of events that are positioned in different segments of the hierarchy, e.g., terms exist in different System Organ Classes (SOCs) or High Level Group Terms (HLGTs), etc.

The output of the CIOMS SMQ IWG illustrates the value of aggregating disparate terms into a clinically relevant concept. A CIOMS MLG EWG is proposed that would build upon the existing MedDRA hierarchy, International Council for Harmonisation (ICH) recommendations for data displays, experience with SMQs, and current regulatory labeling requirements to expand principles for pragmatic and sustained communication of important medical concepts over time. It is anticipated that CIOMS recommendations would be generally applicable to SARs in all forms of RSI. During this first phase of the proposed EWG activities, it is envisioned that **the deliverable will be a consensus report focused on principles and practices for non-binding use of MLGs.** Examples of several MLGs may be constructed for illustrative purposes. Once consensus is achieved on the principles, it is anticipated that the proposed EWG will assess feasibility, implications, and value of developing specific MLGs for broad stakeholder evaluation. This will inform possibilities for a future second phase, i.e., development and testing of proposed MLGs according to the agreed principles. The established ICH process will be engaged for endorsement of this project.

Statement of the Perceived Problem

The granularity of MedDRA (e.g., nearly 23,000 PTs), may have several distinct PTs available that represent closely similar or clinically-related concepts, with the risk that the estimate of the frequency of a SAR in clinical trial data may appear to be diluted when described, as is, in the RSI.
Current approaches to presenting clinically similar SARs in RSI are not consistent product-to-product: in some instances, distinct PTs for the same SAR are grouped in the RSI, whereas in other instances, these PTs are presented separately. For example, clinical descriptions and laboratory results are often presented separately in RSI; hyperkalaemia and blood potassium increased are related, but usually not

[1] Includes only three PTs (v 21.0): PT *Nephrocalcinosis* (10029146), PT *Nephrolithiasis* (10029148), PT *Stag horn calculus* (10041900)

linked in RSI. Regulatory guidelines[2,3] recommend, as good practice, grouping terms in RSI that represent a single SAR (see Appendix I). However, there are no agreed consensus conventions or specific guidelines that describe which terms may be appropriate to group in the RSI to clearly and accurately represent a unique medical concept. If distinct coded terms for the same SAR are presented separately in RSI, a true effect may be diluted or obscured and not adequately communicated to the healthcare community. This principle of grouping PT terms that describe the same or similar SAR, although with a different specificity/sensitivity, also applies to searches and presentation of MedDRA-coded data during analysis. If such terms are not combined in medically meaningful ways, it can be unnecessarily challenging to interpret data displays in a study report, an Integrated Summary of Safety (ISS), or a benefit-risk assessment. These data must be subsequently distilled and condensed from large datasets to display in RSI that can communicate important safety concepts to healthcare providers.

Issues to be Resolved

Acknowledging regional differences in the practice of medicine, an internationally-agreed consensus approach is needed to support (a) Identification of MLG-appropriate medical concepts and (b) Development of durable terms for RSI. RSI is based on data available at the time the respective labeling is developed. Of course, RSI can be modified as new data accumulate. The potential for disagreement on which PTs should be included in RSI, may be counter-productive and can potentially undermine the international consensus, so principles or "rules" for working are needed. For instance, it may be desirable to cluster "sedation, somnolence, drowsiness" in prescriber-oriented RSI rather than list each term separately.

Thus, there needs to be a focus on designating a concise and accurate representation of a SAR for clinicians. The content of an MLG would, where appropriate, be product-independent to allow safety data comparisons, such as is the case with SMQs. Thus, conceptually, a parallel could be drawn between SMQs and MLGs, both of which are intended as tools for harmonization and simplification. SMQs are generally applied for initial screening of MedDRA coded data for potential safety signals. After further review and analysis of the safety data, MLGs, as applicable, would be applied to present the SARs in RSI as a defined grouping of clinically synonymous PTs for each SAR. To be transparent, provide explanation, and prevent loss of specificity, the linkages of the presented SARs to underling MedDRA PTs would need to be documented in the RSI.

Background to the Proposal

The ICH facilitates the use of MedDRA in regulatory activities in all clinical phases of drug development, including product labeling. For labeling, it is generally recommended that clinically important adverse effects are represented as either individual or grouped MedDRA PTs (see Appendix I).

Thus, from the clinical perspective, MedDRA terms that reflect the same clinical entity can be clustered or grouped or a simple summary term, such as "headache" can be selected to simplify and improve the clarity of the medical concept (see Appendix II). Details of the content of an MLG should be provided so

[2] A guideline on Summary of Product Characteristics (SmPC) September 2009, available at http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
http://www.meddra.org/sites/default/files/guidance/file/9610-1910_datretptc_r3_12_sep2016.pdf
[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

that specificity of the medical concept is not lost. When considered together, these grouped terms may be referred to as MLGs.

Each version of the ICH *MedDRA Data Retrieval and Presentation: Points to Consider*[4] document emphasizes the importance of displaying and grouping medically-related concepts when presenting estimates of the occurrence of an event[2,3,5].

Consensus guidelines for data aggregation in RSI would support a standardized, meaningful, reproducible, and consistent aggregation/compilation of safety information. Principles for MLGs would be expected to support processes related to safety information, e.g., for the creation and maintenance of Investigator Brochures, Listedness tables in pharmacovigilance, and Company Core Data Sheets, or Safety Label information. Consumer-oriented labeling may be considered in the future, in a subsequent project as the relevant consensus project on MLG principles matures.

As envisioned, an MLG would represent a SAR in a way that is expected to give the most accurate and understandable description (including standardized product information) to health care providers and other stakeholders. MLGs would be internationally available, support standardized work efforts, and facilitate comparability of safety data from different repositories, even across regulatory jurisdictions.

MLGs would help regulators, policy makers, health care providers, and patients:

- Facilitate decision-making consensus, not only for RSI, but also other communications that can be used worldwide; and
- Communicate medical concepts at a practical and sustainable level of granularity.

RSI develops and evolves over time, e.g., the Investigator Brochure is reviewed at least annually, although sustainability of MLGs is important, thus, it is contemplated that any minor changes in MLGs would not automatically trigger modifications in RSI. Consensus guidelines on MLG development would simplify the approach used across RSI and permit a more standardized result in product-to-product regulatory descriptions. This would enhance comparability of labeled SARs within and between companies, between companies and regulators, as well as in international forums, including medical literature. The groupings can also facilitate considerations in benefit-risk assessments, particularly in instances when modification of RSI is being contemplated.

Type of Expert Working Group and Resources

This is conceived as a public-private partnership. The effort ideally could be organized and coordinated by CIOMS using the well-established CIOMS consensus process that brings together an equitable balance of senior scientists from, for example:

- International biopharmaceutical companies;
- Regulators;
- Academic institutions.

[4] https://www.meddra.org/sites/default/files/guidance/file/000100_termselptc_r4_14_sep2017_0.pdf
[5] http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/monograph/pm-guid-ld-mp-eng.pdf

As mentioned above, the successful CIOMS SMQ output serves as an ideal precedent for creating MLGs because it has a decade of operational history, experience in international consensus and the grouping concepts for MLGs are related to the SMQs.

Timing

If this project is endorsed, it is envisaged that the coordinator, e.g., CIOMS (proposed), will invite experts and form a Working Group within three months of endorsement. Within the following three-months, a work plan with timeline and milestones will need to be agreed. The first phase, i.e., development of principles and guidelines for application of non-binding MLGs would be completed within the following 24-months. Two face-to-face meetings of the proposed EWG are contemplated per annum, supplemented by virtual meetings. If a decision is taken to pursue development of actual MLGs, an extended work plan would be developed at that time.

Appendix

I) Relevant Regulatory Guidance

The use of MedDRA by all pharmacovigilance stakeholders is required in the European Union for the "classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medical product information[6]".

As regards the presentation of safety data in the label of medicinal products, the *Guideline on Summary of Product characteristics (SmPC)*[7] more specifically recommends that adverse drug reactions (ADRs) should be usually represented as a tabulated list at PT level, under the relevant MedDRA SOC, although in exceptional cases different levels of the MedDRA hierarchy or adaptations of MedDRA terms may be used.

Taking into consideration the granularity of MedDRA (e.g., almost 23, 000 PTs in v. 21.0), several distinct PTs may be available in different sections of the terminology to represent the same or clinically-related concepts, with the risk that the estimate of the frequency of an ADR may be impacted and that a safety concern may be diluted in the RSI through the use of these various descriptors in different hierarchical locations.

The need to cluster together distinct MedDRA PTs which represent one SAR has been recognized for many years and the topic was initially discussed during the Blue Ribbon Panel 2006, and, subsequently, at the ICH MedDRA Management Board.

The ICH *MedDRA Data Retrieval and Presentation: Points to Consider* document[8] discusses the importance of displaying and grouping medically-related concepts when presenting estimates of the occurrence of an event.

In the EU, the *Guideline on Summary of Product Characteristics* advises applicants that when presenting ADRs in the label, "*Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, reactions that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms*". While presenting estimate of frequency of the occurrence of a specific ADR from systematic studies, the guidance warns that "*if 'postural dizziness', 'exertional dizziness' and 'unspecified dizziness' were each reported by 2% of patients, this might reasonably be represented in the SmPC as 'Dizziness' occurring in 6% of patients (assuming that only one report of dizziness applied to each patient)*".

[6] Commission Implementing regulation (EU) No 520/2012 of June 2012, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
[7] A guideline on Summary of Product Characteristics (SmPC) September 2009, available at http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[8] http://www.meddra.org/sites/default/files/guidance/file/9610-1910_datretptc_r3_12_sep2016.pdf

A similar approach is followed in the US. In its *Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*[9] (January 2006), the FDA states that within the label "*Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction".*

[9] Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

Appendix

II) Example of Grouping MedDRA Terms via the MedDRA Hierarchy

The following example for the unique medical concept "headache" is presented to illustrate use of the MedDRA hierarchy and some of the associated limitations.

Although it is acknowledged that the existing MedDRA hierarchy provides the opportunity to cluster together terms that convey related medical concepts by resorting to a superordinate MedDRA level, e.g., HLT, it should be considered that the intrinsic level of detail in the MedDRA hierarchy poses significant challenges when it is desired to group medically-related concepts in RSI.

For instance, when representing an accepted medical concept in the RSI, such as "Headache", one would initially evaluate if the superordinate MedDRA HLT *Headaches NEC* adequately represents the concept. However, upon further scrutiny, it is apparent that many PTs grouped under this HLT would not be considered fit for purpose, because they represent other diagnosis where headache is only a symptom, or specific etiologies or syndromes, while at the same time additional PTs grouped under different HLTs might be considered appropriate.
The example below illustrates that the PTs that could be included in the RSI and be part of a proposed MLG *Headache* are a subset of the HLT *Headaches NEC* and also include a term from HLT *Neurological signs and symptoms NEC.*

Note: In the table below, (p) designates terms that are in the primary SOC and (s) designates terms that are in a secondary SOC (MedDRA v21.0).

IIa) Example MLG *Headache*:

No	PT Name/ Inclusion	HLT (p)	HLGT (p)	SOC (p)
1	Drug withdrawal headache	Headaches NEC	Headaches	Nervous system disorders
2	Exertional headache	Headaches NEC	Headaches	Nervous system disorders
3	Head discomfort	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
4	Headache	Headaches NEC	Headaches	Nervous system disorders
5	Medication overuse headache	Headaches NEC	Headaches	Nervous system disorders
6	New daily persistent headache	Headaches NEC	Headaches	Nervous system disorders
7	Primary headache associated with sexual activity	Headaches NEC	Headaches	Nervous system disorders
8	Sinus headache	Headaches NEC	Headaches	Nervous system disorders
9	Tension headache	Headaches NEC	Headaches	Nervous system disorders
10	Vascular headache	Headaches NEC	Headaches	Nervous system disorders
No	**PT Name/ Exclusion**	**HLT (p)**	**HLGT (p)**	**SOC (p)**
1	Thunderclap headache	Headaches NEC	Headaches	Nervous system disorders
2	Cervicogenic headache	Headaches NEC	Headaches	Nervous system disorders
3	Neck pain	Musculoskeletal and connective tissue pain and discomfort	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal and connective tissue disorders
4	Occipital neuralgia	Headaches NEC	Headaches	Nervous system disorders
5	Cluster headache	Headaches NEC	Headaches	Nervous system disorders
12	Chronic paroxysmal hemicrania	Headaches NEC	Headaches	Nervous system disorders

13	Cold-stimulus headache	Headaches NEC	Headaches	Nervous system disorders
14	Postictal headache	Headaches NEC	Headaches	Nervous system disorders
15	Paranasal sinus discomfort	Upper respiratory tract signs and symptoms	Respiratory tract signs and symptoms	Respiratory, thoracic and mediastinal disorders
16	Post lumbar puncture syndrome	Neurological and psychiatric procedural complications	Procedural related injuries and complications NEC	Injury, poisoning and procedural complications
17	Post-traumatic headache	Headaches NEC	Headaches	Nervous system disorders
18	Procedural headache	Neurological and psychiatric procedural complications	Procedural related injuries and complications NEC	Injury, poisoning and procedural complications
19	Ophthalmoplegic migraine	Headaches NEC	Headaches	Nervous system disorders
20	Typical aura without headache	Headaches NEC	Headaches	Nervous system disorders
21	Temporal arteritis	Arterial inflammations	Vascular inflammations	Vascular disorders
22	Premenstrual headache	Menstruation and uterine bleeding NEC	Menstrual cycle and uterine bleeding disorders	Reproductive system and breast disorders
23	Primary cough headache	Headaches NEC	Headaches	Nervous system disorders
24	Sinus pain	Headaches NEC	Headaches	Nervous system disorders
25	PTs from HLT Migraine headaches	Migraine headaches	Headaches	Nervous system disorders
26	Craniocervical syndrome	Headaches NEC	Headaches	Nervous system disorders
27	Eagle's syndrome	Bone related signs and symptoms	Bone disorders (excl congenital and fractures)	Musculoskeletal and connective tissue disorders
28	SUNCT syndrome	Headaches NEC	Headaches	Nervous system disorders
29	Temporomandibular joint syndrome	Joint related disorders NEC	Joint disorders	Musculoskeletal and connective tissue disorders

IIb) Alternative display of example MLG *Headache*:

HLT	PT	Scope
Headaches NEC	Drug withdrawal headache (p)	In
	Exertional headache (p)	In
	Headache (p)	In
	Medication overuse headache (p)	In
	New daily persistent headache (p)	In
	Primary headache associated with sexual activity (p)	In
	Sinus headache (p)	In
	Tension headache (p)	In
	Vascular headache (p)	In
	Cervicogenic headache (p)	Out
	Chronic paroxysmal hemicrania (p)	Out
	Cluster headache (p)	Out
	Cold-stimulus headache (p)	Out
	Craniocervical syndrome (p)	Out
	Eagle's syndrome (s)	Out
	External compression headache (p)	Out
	Occipital neuralgia (p)	Out
	Ophthalmoplegic migraine (p)	Out
	Postictal headache (p)	Out
	Post lumbar puncture syndrome (s)	Out

	Post-traumatic headache (p)	Out
	Premenstrual headache (s)	Out
	Primary cough headache (p)	Out
	Procedural headache (s)	Out
	SUNCT syndrome (p)	Out
	Stroke-like migraine attacks after radiation therapy (s)	Out
	Temporomandibular joint syndrome (s)	Out
	Thunderclap headache (p)	Out
	Typical aura without headache (p)	Out
Neurological signs and symptoms NEC	Head discomfort (p)	In
	Abulia (s)	Out
	Activation syndrome (s)	Out
	Agitated depression (s)	Out
	Agitation (s)	Out
	Agitation neonatal (s)	Out
	Agitation postoperative (s)	Out
	Apnoeic attack (s)	Out
	Apparent life threatening event (s)	Out
	Bezold-Jarisch reflex (s)	Out
	Binocular eye movement disorder (s)	Out
	Camptocormia (p)	Out
	Cerebrospinal fluid leakage (p)	Out
	Chronic tic disorder (s)	Out
	Clonus (p)	Out

Complex tic (s)	Out
Crying (s)	Out
Decerebrate posture (p)	Out
Decorticate posture (p)	Out
Decreased eye contact (s)	Out
Decreased nasolabial fold (s)	Out
Disorientation (s)	Out
Dizziness (p)	Out
Dizziness exertional (p)	Out
Dizziness postural (p)	Out
Drooling (p)	Out
Exaggerated startle response (p)	Out
Eye movement disorder (s)	Out
Foaming at mouth (s)	Out
Fontanelle bulging (p)	Out
Fontanelle depressed (p)	Out
Froin's syndrome (p)	Out
Gait deviation (s)	Out
Gait disturbance (s)	Out
Gait inability (s)	Out
Gaze palsy (s)	Out
Grimacing (p)	Out
Heterophoria (s)	Out
Hyporesponsive to stimuli (p)	Out

	Inability to crawl (p)	Out
	Intracranial hypotension (p)	Out
	Locomotive syndrome (s)	Out
	Meningism (p)	Out
	Mobility decreased (s)	Out
	Myoclonus (p)	Out
	Neonatal behavioural syndrome (p)	Out
	Neuroglycopenia (p)	Out
	Neurological decompensation (p)	Out
	Neurological symptom (p)	Out
	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (s)	Out
	Persistent postural-perceptual dizziness (p)	Out
	Personality change (s)	Out
	Pleocytosis (p)	Out
	Pneumocephalus (s)	Out
	Post concussion syndrome (s)	Out
	Post-anoxic myoclonus (p)	Out
	Posture abnormal (s)	Out
	Presyncope (p)	Out
	Procedural dizziness (s)	Out
	Protrusion tongue (s)	Out
	Provisional tic disorder (s)	Out
	Respiratory depression (s)	Out

	Restlessness (s)	Out
	Secondary tic (s)	Out
	Sensory overload (p)	Out
	Slow response to stimuli (p)	Out
	Spontaneous cerebrospinal fluid leak syndrome (p)	Out
	Thinking abnormal (s)	Out
	Tic (s)	Out
	Toe walking (s)	Out
	Tongue biting (p)	Out
	Tongue movement disturbance (s)	Out
	Trigemino-cardiac reflex (p)	Out
	Unresponsive to stimuli (p)	Out

Appendix

III) Example of Mock MLG Documentation (refined approach, perhaps with a template, to be outlined by the proposed EWG)

Note: This example contains fictitious information and is included for illustrative purposes only.

MLG – Definition to be created by proposed EWG

MLG Name: Headache
Possible MedDRA Labeling Grouping Code: MLG_XXXX

Associated SOC Name: Nervous system disorders

Goal:
This MLG includes all relevant PTs that represent the medical condition of *Headache* to aggregate related safety data.

Definition of medical condition:
Headache is defined as “pain in the head” [1]. It is synonymously called cephalgia, cephalalgia or cephalodynia [1].

As “pain” is defined as a more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings [1], also head discomfort is included in this MLG.

Excluded from this MLG are PTs representing migraine, syndromes or diagnoses with the potential symptom headache and headaches with specific underlying causes or diseases, such as Cold-stimulus headache or Post-traumatic headache.

Possible allocations at the PT level:

Inclusion in MLG:

1. PT Drug withdrawal headache
2. PT Exertional headache
3. PT Headache
4. PT Head discomfort
5. PT Medication overuse headache
6. PT New daily persistent headache
7. PT Primary headache associated with sexual activity
8. PT Sinus headache
9. PT Tension headache
10. PT Vascular headache

Possible exclusions from an MLG for “Headache”:

1. PTs under HLT Migraine headaches

2. PT Thunderclap headache
3. PTs representing syndromes or diagnoses with the potential symptom of headache (e.g., PTs Craniocervical syndrome, Eagle's syndrome, SUNCT syndrome, Temporomandibular joint syndrome)
4. PT Cervicogenic headache
5. PT Neck pain
6. PT Occipital neuralgia
7. PT Cluster headache
8. PT Chronic paroxysmal hemicrania
9. PT Cold-stimulus headache
10. PT Postictal headache
11. PT Paranasal sinus discomfort
12. PT Post lumbar puncture syndrome
13. PT Post-traumatic headache
14. PT Procedural headache
15. PT Ophthalmoplegic migraine
16. PT Typical aura without headache
17. PT Temporal arteritis
18. PT Premenstrual headache
19. PT Primary cough headache
20. PT Sinus pain

Additional considerations:

MedDRA version 14.1 considerations:
Currently, no specific MedDRA considerations have been identified.

MedDRA version 16.0 considerations:
LLT Premenstrual headache was promoted to PT level (PT Premenstrual headache) and not included in this MLG.

MedDRA version 17.1 considerations:
LLT Paranasal sinus discomfort was previously under PT Sinus headache, which is included in this MLG. With MedDRA version 17.1 LLT Paranasal sinus discomfort was promoted to PT level (PT Paranasal sinus discomfort) and not included in this MLG.

Example for documenting MLG history:

- MLG *Headache* was originally defined in MedDRA v8.0
- Documentation was first provided in MedDRA v14.1

- Additions and deletions of PTs:

PT Additions	PT Deletions	MedDRA Version
PT Cluster headache PT Drug withdrawal headache PT Headache PT Postictal headache PT Sinus headache PT Tension headache		8.0
PT Hemicephalalgia		11.0
PT Exertional headache		11.1
PT Head discomfort PT Vascular headache	PT Cluster headache PT Hemicephalalgia (demoted under PT Headache) PT Postictal headache	14.1
PT Medication overuse headache		15.1
PT New daily persistent headache		18.1
PT Primary headache associated with sexual activity		20.0

- MedDRA v20.1:
  MedDRA Labeling Grouping documentation updated to new format standard without changes in definition of medical condition or in-/ exclusion criteria
- Updates for exclusion criteria, not covered explicitly by definition, inclusion and/or exclusion criteria:
  MedDRA v19.1:
  PT Sinus pain added.

MLGs and SMQ; related MedDRA Medical Term Groupings (may not be a complete list):

- MLG Eye pain and eye discomfort
- MLG Feeling unwell
- MLG Migraine
- MLG Sinusitis and sinus congestion
- SMQ Convulsions
- SMQ Drug abuse and dependence
- SMQ Drug withdrawal

References

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2. http://www.merckmanuals.com/professional/neurologic-disorders/craniocervical-junction-abnormalities/craniocervical-junction-abnormalities, assessed Apr 22, 2016