

## MedDRA Blue Ribbon Panel 7 – Proposed Revisions to the Neoplasm SOC: Orientation to the Topic

### Purpose

This document provides information about the topic for the MedDRA Blue Ribbon Panel (BRP7) on proposed revisions for SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. For brevity's sake, in this document, the SOC will be referred to as the "Neoplasm SOC".

### Background

The Neoplasm SOC is one of the largest of the 26 MedDRA SOC's; its rate of growth roughly parallels that of the terminology overall. The table below shows the growth of the Neoplasm SOC over the years.

**Table 1. Growth of MedDRA**

MedDRA Version							
	2.1	3.0	4.1	6.0	9.0	12.0	13.1
LLT	6299	6339	6922	7269	7662	7873	7876
PT	1338	1361	1570	1632	1629	1695	1699
HLT	200	200	198	196	196	203	203
HLGT	40	40	40	40	40	40	40
<b>Total</b>	<b>7877</b>	<b>7940</b>	<b>8730</b>	<b>9137</b>	<b>9527</b>	<b>9811</b>	<b>9818</b>

For the past several years the MSSO has considered changes to the Neoplasm SOC but users have not shown much interest. More recently a MedDRA user contacted the MSSO with a proposal for a set of fundamental changes to the Neoplasm SOC. The MSSO has discussed the proposed changes at a number of user meetings, and the feedback to date has been positive. Users generally express the opinion that a more detailed exploration of the proposals would be useful, and they support the idea of a BRP to address the proposals.

### Cancer therapeutics and MedDRA

The biopharmaceutical industry's approach to developing therapies for malignant neoplasms has changed [significantly in the past several years](#). In prior decades, cytotoxic drugs were used broadly against a variety of tumor types. Off label use of traditional cytotoxic therapies was the norm, not the exception.

More recently, the approach to cancer therapy has exploited the explosion of knowledge of the human genome and of the genetic anomalies that underlie various tumors. Therapies are now developed that target a specific genetic characteristic (e.g., HER-2 for breast carcinomas) in a specific histologic sub-type of tumor.

Pathologists – physicians who make the tissue diagnosis of malignancy – have for a long time focused on classification of tumors not only in terms of benign and malignant

forms but also on general tissue types (sarcomas, carcinomas, etc.) and sub-types (papillary, ductal, etc.). In the past, such classifications had been based largely on the histology of the tumor. In modern pathologic practice, the genetics of a tumor complement the specific histologic diagnosis and help guide therapy.

For example, a diagnosis of a “non-small cell lung carcinoma” is now also investigated for epithelial growth factor receptor (EGFR) activity, and the therapy is modulated according to the patient’s EGFR status. This has resulted in improved survival rates for a tumor that, in the past, had a very dismal prognosis.

MedDRA’s Neoplasm SOC was developed while such changes in therapeutic approaches were beginning to take hold, but the SOC has remained largely unchanged in its basic structure. Part of the reason for this BRP topic is to determine to what extent the Neoplasm SOC needs to be revised to align itself with modern cancer therapeutic development.

## Orientation to the Panel’s Task

In the following section, specific proposed changes are presented. Panelists are asked to consider the utility and impact of the proposed changes for both coding/classifying information and on retrieval and analysis of these data. Please keep in mind how the Neoplasm SOC is used by the MedDRA community, e.g., to code indications, AEs/ADRs, or for other uses (e.g., to reconcile data coded in other terminologies).

The Panel may choose to agree with any one of these proposals, all of them, or none of them. They may also recommend to refine the proposals as they see fit.

## Proposed changes

The proposals are:

1. Move “cyst” terms from Neoplasm SOC and keep them only in their “site of manifestation” SOC. Note that, from a mechanistic viewpoint, the MSSO would remove the secondary link of most “cyst” terms and keep only their remaining primary links. For example, PT *Bone cyst* would lose its secondary link to the Neoplasm SOC but would retain its current primary link to SOC *Musculoskeletal and connective tissue disorders*.

The rationale underlying this is that “cyst” is an anatomic designation which only very rarely confers the quality of “neoplasia” (abnormal growth of cells).

A point to consider in reviewing this proposal is whether or not **analysis** of data coded with terms in the Neoplasm SOC would be enhanced, made more difficult, or remain the same as it is now. From a purely medical point of view, “delinking” most “cyst” terms from the Neoplasm SOC makes sense as very few cysts are de facto neoplastic. Approximately 100 “cyst” PTs in the Neoplasm SOC – along

with their associated LLTs – would be impacted by this proposal without major impact to cumulative data output in a primary SOC view. The Panel is asked to weigh the risks and benefits to balance medical correctness against the impact to legacy and future coded data.

**Question 1A:** Does the Panel recommend making this change to the “cyst” terms in MedDRA?

**Question 1B:** If the Panel does not recommend making this change, does it have another recommendation? Or should the “cyst” terms remain in their current location in the Neoplasm SOC?

2. Place more specific histologic tumor types on the PT level. Currently, some specific histologic subtypes of various benign and malignant tumors are at the LLT level, but in some cases, particular subtypes are missing.

For example, terms such as PT *Benign lung neoplasm* are in MedDRA, but more specific subtypes such as “Alveolar adenoma of lung” are currently not.

The rationale for this proposal is that, increasingly, oncologic therapies are being targeted at specific histologic types of tumors (e.g., variants of non-small cell lung carcinoma) often combined with a genetic profile of the neoplasm (e.g., epithelial growth factor receptor positivity). The increased degree of specificity in MedDRA would allow for aggregation and analysis of specific tumor types.

The impact to MedDRA is difficult to gauge but could represent thousands of terms, including promotion of existing LLTs representing histologic subtypes and adding (in a proactive way) terms for subtypes that are not in MedDRA currently. In MedDRA v13.1, there were 1909 PTs and 8383 LLTs in the Neoplasm SOC; not all LLTs and PTs may be affected, but these numbers are at least an approximation of the potential magnitude of the changes.

This proposal would also closely align with proposal no. 3 described below.

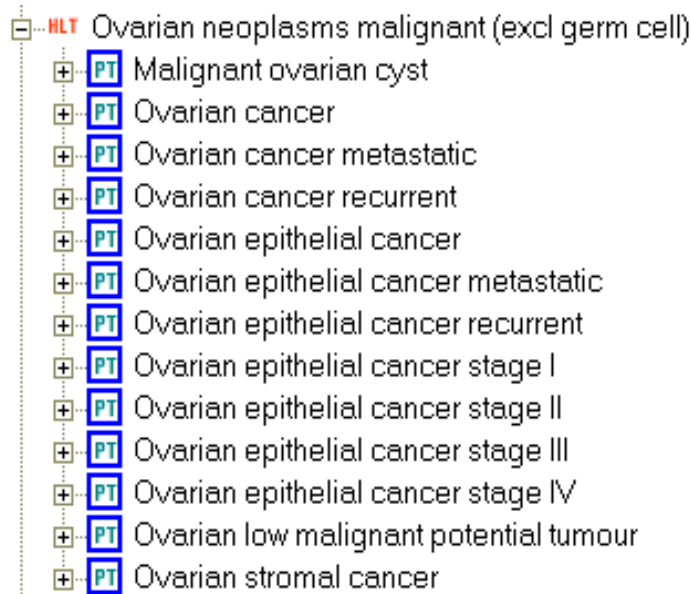
Note that this proposal may result in some LLT promotions as well as addition of terms to the PT level.

It is well known that for some safety reports, especially from spontaneous sources, the exact tumor type may not be known. For example, a patient may report that she has “breast cancer” but may be unaware that she has a medullary carcinoma, infiltrating ductal carcinoma, etc. For this reason, the MSSO recommends that the relatively “broad” terms for neoplasms (e.g., PT *Breast cancer*) remain in MedDRA; in other words, if there is a decision to increase the number of highly specific terms at the PT level, this should not be at the expense of the existing broader concepts.

Currently in MedDRA, PTs for many malignant neoplasms include information about the stage of the tumor (a clinical assessment) while only a handful of terms cite the grade of a tumor (a histologic assessment). The Panel is asked to consider how MedDRA should handle existing “stage” terms (e.g., PT *Cervix carcinoma stage III*).

An example of a typical set of existing “stage” PTs in the Neoplasm SOC is shown below:

**Figure 1: “Stage” PTs in MedDRA**



**Question 2A:** Should the MSSO add specific histologic subtypes of neoplasms to the PT level?

**Question 2B:** If the answer to 2A is yes, please comment on the most optimal approach (Add terms proactively? Allow terms to be populated through the Change Request process? Add terms in one MedDRA release or over multiple releases? Another approach?)

**Question 2C:** If the answer to 2A is yes, what should be the fate of the existing “stage” terms in MedDRA (currently at the PT level)? [Note: for the purposes of this question, “stage” terms also include “metastatic” and “recurrent” qualifiers].

**Question 2D:** Please address in general how the increased granularity resulting from this proposal will affect coding and retrieval. Particularly for coding, how would one handle a term describing a specific lung tumor and its EGFR status?

3. Update the terms in the Neoplasm SOC according to standard tumor classification systems. There are many tumor classification systems (e.g., French-American-British [FAB] classification for acute leukemia). The World Health Organization (WHO) has drafted classification systems for neoplasms in many – but not all – organ systems; these classifications are widely accepted by pathologists and oncologists. These classification systems evolve and change over time; this needs to be considered when anticipating the maintenance of such classifications in MedDRA.

The names of some neoplasms currently in MedDRA may not be up-to-date with accepted classifications (e.g., PT/LLT *Cystosarcoma phyllodes* in MedDRA; the more accepted name for this benign neoplasm is “phyllodes tumor”). And, referring to proposal no. 2, there are gaps in MedDRA where many neoplasms listed in standard classifications systems are missing.

The rationale and impact for this proposal are similar to those for proposal no. 2. In particular, if the “gaps” of missing histologic subtypes were to be filled, the increase in PTs could number in the hundreds. Additionally, existing MedDRA terms that are out of date with current classifications would need to be addressed (probably be made into non-current LLTs).

There are two possible considerations for action here: if the Panel answers yes to Question 2A, then standard tumor classification systems could be used as the basis for the addition of new specific histologic sub-type terms. A more limited approach – if the Panel does not recommend to go forward with the actions in Question 2 – is for the MSSO to identify and update the existing neoplasm terms in MedDRA to make them consistent with modern neoplasm classification systems.

Below is an example of how part of the Neoplasm SOC may look if a standard tumor classification system for malignant lung neoplasms is applied:

SOC	HLGT	HLT	PT	LLT
				Neoplasms benign, malignant and unspecified (incl cysts and polyps)
				Respiratory and mediastinal neoplasms malignant and unspecified
				Lung neoplasms malignant
				Adenocarcinoma of lung
				Adenocarcinoma acinar of lung
				Adenocarcinoma of lung with mixed subtypes
				Adenocarcinoma papillary of lung
				Bronchioloalveolar carcinoma mucinous
				Bronchioloalveolar carcinoma nonmucinous
				Bronchioloalveolar ixed mucinous and non-mucinousor intermediate cell type
				Clear cell adenocarcinoma of lung
				Mucinous ("colloid") adenocarcinoma of lung
				Mucinous cystadenocarcinoma of lung
				Signet-ring adenocarcinoma of lung
				Solid adenocarcinoma of lung with mucin
				Well-differentiated fetal adenocarcinoma of lung
				Lung neoplasm malignant
				Lung cancer
				Lung neoplasm malignant NOS
				Small cell carcinoma of lung
				Combined small cell carcinoma of lung
				Squamous cell carcinoma of lung
				Squamous cell carcinoma basaloid of lung
				Squamous cell carcinoma clear cell of lung
				Squamous cell carcinoma papillary of lung
				Squamous cell carcinoma small cell of lung

**Question 3A:** Should standard neoplasm classification systems (e.g., WHO classifications) be used as the basis for neoplasm terms in MedDRA?

### What to expect

Recommendations made by the Panel will be reviewed by the MedDRA Management Board who will have the final say in directing the MSSO to proceed – or not – with the Panel’s recommendations.

### Proposed timeline

April 2011 – Blue Ribbon Panel conducted

May 2011 – Panel recommendations drafted

June 2011 – MedDRA Management Board reviews recommendations

Depending on the extent of changes recommended by the Panel (and if approved by the Board), the MSSO will institute changes beginning in MedDRA v15.0 (release date 1 March 2012) and possibly spanning additional versions.