



# MedDRA<sup>®</sup> Modifiers

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9 April 2004



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## MedDRA Modifiers

### 1 Introduction

One of the consistent issues related to MedDRA's maintenance has been the request for specific terms that have a modifier term associated with them. A modifier, in this context, is a word or phrase that is used in conjunction with a MedDRA term to modify its meaning. Examples of modifiers include aggravated, acute, prolonged, etc. For the purposes of this paper, the MedDRA term used in conjunction with a modifier is a "base term." A combination of a MedDRA base term and modifier is represented as "base term + modifier."

In the course of MedDRA maintenance, the MSSO frequently receives requests to add specific terms that include a modifier (e.g., prolonged neutropenia). Currently, in many cases, these types of requests are being rejected because the term is not a new unique concept in MedDRA and is sufficiently addressed by an existing term. Another consideration for rejecting such requests relates to the stabilization effort to control the growth of MedDRA. Requests for modified terms have the potential to greatly expand the size of MedDRA if certain limits were not put in place to prevent this type of expansion.

Nonetheless, the MSSO understands that most organizations that make requests for the addition of new terms that include modifiers do so because they have a company-specific need that is not currently fulfilled by MedDRA. The MSSO's function is to review each request in the context of the scope and intent of MedDRA as well as the need for the new term. As mentioned previously, in most cases, these types of requests are being rejected. Since this can serve to limit the utility of MedDRA for some users, the MSSO proposes to implement a new concept in MedDRA – MedDRA modifiers.

MedDRA modifiers would be an additional file or set of files that would be distributed with MedDRA. The current distribution files would not be changed and, therefore, any current software that loads MedDRA would not be affected. The use of modifiers would be optional for subscribers although they will also likely become E2B data fields. An organization could apply any modifier to any existing MedDRA term for the purposes of coding. In some cases, a particular combination of modifier and base term may be inappropriate (e.g., chronic death) and the MSSO envisions an extension of the ICH "*MedDRA Term Selection: Points to Consider*" document to address these types of issues.

The concept of MedDRA modifiers raises several implementation issues that will be addressed by this paper. They include the following:

- If the use of a modifier in conjunction with a MedDRA base term changes the meaning or concept of the base term, is that appropriate? For example, if the base term is "angina pectoris" and a potential modifier of



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“prophylaxis of” is applied, the new term “prophylaxis of angina pectoris” has a different meaning than the original base term.

- To which term level(s) does(do) modifiers apply?
- What should be done with existing MedDRA base terms that contain potential modifiers (e.g., *Exacerbation of acne*, *Acute leukaemia NOS*)?
- What is the impact of modifiers on MedDRA hierarchy terms (HLT, HLG, and SOC) that include modifiers (e.g., *HLT Acute polyneuropathies*).
- Given that MedDRA has been in use for several years, what is the MSSO’s proposed conversion approach to minimize the impact to subscribers with existing MedDRA-coded data?
- MedDRA is a component of the E2B standard. What existing MedDRA E2B fields should include modifiers and how should these fields be structured?
- The concept of modifiers has a significant impact on analysis and reporting. What is the impact and what are methods of dealing with this impact?
- While the creation of modifiers will potentially reduce the number of change requests to the MSSO, what are the benefits for the MedDRA user community?

As shown with the topics mentioned above, the implementation of modifiers could have a significant impact on the current use of MedDRA in many areas to the point of creating a “new MedDRA.” One of the goals of this paper is to define the scope of the use of modifiers within MedDRA. Taken to an extreme, the use of modifiers could significantly reduce the number of MedDRA base terms and many current base terms would become a combination of a modifier and a base term. SOC *Investigations*, for instance, could be significantly reduced in number of terms if words like “increased,” “decreased,” “normal,” and “abnormal” become modifiers. This could create a very large set of non-current LLTs. The concept of currency may also have to be reviewed.

The process employed in developing this paper was to not initially exclude any option for the implementation of modifiers in MedDRA. As the modifier concept evolves and conclusions are developed, the MSSO’s proposed scope will become clarified and defined. Implementation options that eventually are rejected will be maintained in the document for reference purposes.



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## 2 Benefits of Modifiers and “New MedDRA” to the User Community

MedDRA has grown at a rapid pace since its official release in 1999 (Table 1). Although the user community generally has expressed satisfaction with the greater size and specificity of MedDRA compared to older terminologies, some users have cautioned that a terminology of such a large size could result in data so widely scattered among precise concepts that “signals” could be lost, or at least, difficult to detect. To some extent, this concern is being addressed with the development of Standardised MedDRA Queries (SMQs).

**Table 1**

No. of Terms per Hierarchy Level	Version 1.5	Version 2.1	Version 7.0
SOC	26	26	26
HLGT	88	334	332
HLT	653	1663	1681
PT	8658	11,193	16,449
LLT	35,335	46,258	61,204

Nonetheless, the user community continues to submit requests for ever more precise and complex concepts to be added to MedDRA. In an effort to balance the needs of the end users against over-expansion of the terminology, the MSSO has had to adopt several measures to limit the growth of MedDRA (rejecting terms based on laterality alone, adopting a policy to determine which “prophylaxis” terms can be added, etc.). The use of the “base term + modifier” paradigm for coding may help both the user community and the MSSO to achieve the balance of growth while expanding coding flexibility.

For example, the candidate modifier “acute” could be applied to virtually any medical condition term currently in MedDRA, greatly expanding the number of coding possibilities without increasing the size of MedDRA to any significant extent. There is currently a LLT *Oculomotor paralysis*; if a company should receive a verbatim report of “acute onset of oculomotor paralysis,” the coder would be able to pair up the modifier “acute” with the base term of “oculomotor paralysis” to very precisely represent the reporter’s verbatim concept. Below, in addition to “oculomotor paralysis,” are some examples of the greater specificity obtainable:



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**Table 2**

Verbatim	Modifier	Base term	“Interpretation”
Acute onset of oculomotor paralysis	Acute	Oculomotor paralysis	Acute oculomotor paralysis
Patient is frequently confused	Frequent	Confusion	Frequently confused
SGPT GR 4	CTCAE Grade 4 (v3.0)	SGPT	Grade 4 (CTCAE v3.0) SGPT elevation
Halitosis got worse	Aggravated/worsened/exacerbated	Halitosis	Halitosis worsened

The most significant potential benefit to the end user of MedDRA is less reliance on the “best fit” for matching a verbatim to MedDRA term(s) and more chances for an “exact match.” This will be especially helpful for a variety of concepts that, even with MedDRA’s current degree of specificity, are still awkward to codify. For example, version 3.2 of the “*MedDRA Term Selection: Points to Consider*” (PTC) document currently recommends coding an “aggravated” pre-existing condition verbatim to the “aggravated” term in MedDRA, if one exists. If no “aggravated” term currently exists, the PTC document recommends either using the unmodified concept OR coding both the unmodified concept AND a qualifying term such as LLT *Condition aggravated*. This can be difficult to achieve in certain databases, and linking of the separate LLT *Condition aggravated* with the unmodified concept in a relational way may not always be possible. In addition, some subscribers may be concerned that it gives the appearance of more than one event and increases the number of event counts. The use of a separate modifier of “aggravated/worsened/exacerbated” in the “base term + modifier” paradigm addresses all these issues in a positive way.

Another example of a current problem that could be greatly ameliorated by adoption of the modifier concept is that of the Common Terminology Criteria for Adverse Events (CTCAE) codes that are widely used in oncology and HIV studies. The current scheme of assigning a mapping of a single MedDRA term for each CTCAE concept + grade is awkward. For example, a CTCAE grade 4 Rash – erythema multiforme term consists of multiple concepts (by MedDRA criteria), e.g., erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis, etc. which are life-threatening or disabling. Currently, for purposes of “cross-talk” mapping of MedDRA and CTCAE codes, only one MedDRA term has been applied to cover these multiple concepts embodied in this “grade 4” code. Companies are reluctant to abandon CTCAE coding in their oncology and HIV studies and have struggled to find solutions to reconcile this coding against their



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MedDRA-coded data. If the list of MedDRA modifiers were to contain “CTCAE Grade X (version x.x)” terms, then the subscribers would be able to faithfully represent the CTCAE-coded concepts without loss of information as is currently the case. For example, the verbatim “allergic gr 3” would now be “Allergic reaction + CTCAE Grade 3 (v3.0),” which can be easily cross-referenced without information loss to the corresponding CTCAE tables.

**Table 3**

Verbatim	Corresponding CTCAE code	Current MedDRA	“New MedDRA”
Fatigue Gr 2	Fatigue (asthenia, lethargy, malaise) – Moderate or causing difficulty performing some ADL	Fatigue	Fatigue + CTCAE Grade 2 (v3.0)
Elevated triglycerides Grade 3	Triglyceride, serum-high (hypertriglyceridemia) – >5.0 – 10 x ULN	Triglycerides high	Triglycerides + CTCAE Grade 3 (v3.0)
Grade 3 ANC	Neutrophils/granulocytes (ANC/AGC) -- <1000 – 500/mm <sup>3</sup> , <1.0 – 0.5 x 10 <sup>9</sup> /L	Absolute neutrophil count decreased	Neutrophil count + CTCAE Grade 3 (v3.0)
Mouth pain/mucositis grade 1	Mucositis/stomatitis – erythema of the mucosa	Mucositis	Mucositis + CTCAE Grade 1 (v3.0)
Diarrhea Grade 4	Diarrhea – Life-threatening consequences (e.g., hemodynamic collapse)	Diarrhea	Diarrhea + CTCAE Grade 4 (v3.0)

The addition of modifiers could also benefit the subscriber community in other ways. Rather than trying to remember the current set of MedDRA rules regarding population-level modifiers, severity modifiers, laterality issues, etc., when recommending a new term for MedDRA, the subscriber may recommend either a base term concept or a modifier that appears to be missing from MedDRA. This might also lead to less “back-and-forth” between the MSSO and the subscriber currently trying to get a particular change request to be accepted.

Importantly, modifiers increase the flexibility for data input while still maintaining MedDRA as a standard terminology. Modifiers would, like base terms, be subject to addition/modification/correction by the subscriber community (via a change request process) and still be subject to the international medical oversight to which current MedDRA is subject. With the addition of a separate modifier list, the terminology maintenance issues are negligible compared with trying to address all user needs for individually modified terms. If the “new MSSO-DI-8289-1.0.0.



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MedDRA" were to contain 25,000 base term concepts, then the addition of a *single* new modifier term to MedDRA increases the number of potential representative concepts by 25,000. In practice, this would probably be less than 25,000 terms as not any one modifier would be expected to apply to all 25,000 base terms. The subscriber receives all the benefit of the greater capacity for verbatim representation with minimal maintenance expenditures for the MSSO.



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### 3 Plan for External Involvement in Development and Review

The implementation of the modifier concept is a significant change to MedDRA that has many different implications. The implications include existing MedDRA-coded data, electronic submissions (i.e., E2B), current IT systems (e.g., clinical and safety systems, autoencoders) and the development of queries and data analysis. Realizing both the benefit and the effort involved in implementing modifiers, the MSSO understands the need to coordinate with many different stakeholder groups including the following:

- MedDRA subscribers
- ICH regulators
- ICH E2B Expert Working Group
- ICH Points to Consider Expert Working Group
- System developers

The decision to implement modifiers and the level of implementation must consider the views from these various organizations. If the decision to implement is made, the schedule of the implementation must be coordinated with these groups so that necessary guidance is in place to support the concept.

The MSSO's plan is to work with each group to communicate the progress of the modifier concept in as many means that are available (e.g. email to subscribers, user group discussion topics, direct participation with the expert working groups, meetings with system developers). The goal of these various communication forms is to disseminate the concept of modifiers, discuss implementation options and, most importantly, collect feedback on the concept. The initial product to be shared is the development of this paper. Subsequent documents and briefings will be necessary to communicate the development of this concept. A key set of points will drive the development of the modifier concept:

- Communicate the concept
- Collect feedback
- If implementation is chosen, provide a reasonable timeframe for implementation

The MSSO believes by following these points the potential implementation of the modifier concept will be well coordinated and well supported for the MedDRA community.



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## 4 Modifier Fields Needed for E2B Message

One of the most obvious points of impact for the modifier concept is the electronic transmission of individual case safety reports or the E2B message. ICH has established an ICH E2B(M) standard for the communication of individual case report reports that specially includes MedDRA. One of the goals of this paper is to make recommendations to the ICH E2B group on specific changes needed to support modifiers.

The issues for the modifier concept and the E2B message include the following:

- To which term level(s) does(do) modifiers apply?
- Would all existing E2B fields that utilize MedDRA currently be revised to allow for modifiers?
- What is the maximum number of modifiers that can be applied to a single E2B field?

Assuming the broadest implementation of modifiers in the context of the E2B message means that all current E2B fields that utilize MedDRA will include a modifier field for both LLT and PT (where applicable). Since the E2B message accommodates the concept of a repeatable field, the E2B message could accommodate multiple modifiers per MedDRA term. A potential logical limit of three modifiers per MedDRA term should be established. It should be noted that the modifier field should be an optional field within the E2B message since it may not be necessary to include a modifier term to properly code an event to MedDRA.

The following E2B message fields highlighted in **bold** require a MedDRA term and therefore an associated modifier field may be necessary.

**Table 4**

Data Element	Sub Data Element
B.1.7.1 Structured information on relevant medical history including onset and resolution date as well as relevant comments	
	B.1.7.1a.1 MedDRA version for medical history
	<b>B.1.7.1a.2 Structured information*</b>
B.1.8 Relevant past drug history	
	B.1.8f.1 MedDRA version for indication



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Data Element	Sub Data Element
	<b>B.1.8f.2 Indication*</b>
	B.1.8g.1 MedDRA version for reaction
	<b>B.1.8g.2 Reaction*</b>
B.1.9.2 Reported cause(s) of death	
	B.1.9.2.a MedDRA version for reported causes(s) of death
	<b>B.1.9.2.b Reported cause(s) of death (repeat as necessary)*</b>
B.1.9.4 Autopsy-determined cause(s) of death	
	B.1.9.4a MedDRA version for autopsy-determined cause(s) of death
	<b>B.1.9.4b Autopsy-determined cause(s) of death (repeat as necessary) *</b>
B.1.10.7 Relevant medical history and concurrent conditions of parent	
	B.1.10.7.1a.1 MedDRA version for parent medical history
	<b>B.1.10.7.1a.2 Structured information*</b>
B.1.10.8 Relevant past drug history	
	B.1.10.8f.1 MedDRA version for indication
	<b>B.1.10.8f.2 Indication*</b>
	B.1.10.8g.1 MedDRA version for reaction
	<b>B.1.10.8g.2 Reactions (if any and known)*</b>
B.2 Reaction(s)/Event(s)	
	B.2.i.1.a MedDRA version for reaction/event term LLT
	<b>B.2.i.1.b Reaction/event in MedDRA terminology (LLT)</b>
	B.2.i.2.a MedDRA version for



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Data Element	Sub Data Element
	reaction/event term PT
	<b>B.2.i.2.b Reaction/event in MedDRA terminology (PT )</b>
B.4.k.11 Indication for use in the case	
	B.4.k.11a MedDRA version for indication
	<b>B.4.k.11b Indication for use in the case*</b>
B.4.k.17.2 Effect of rechallenge (or re-exposure), for suspect drug(s) only	
	B.4.k.17.2a MedDRA version for reaction(s)/event(s) recurred
	<b>B.4.k.17.2b If yes, which reaction(s)/event(s) recurred?*</b>
B.4.k.18.1 Relatedness of drug to reaction(s)/event(s)	
	B.4.k.18.1a MedDRA version for Reaction assessed
	<b>B.4.k.18.1b Reaction assessed*</b>
B.5.3a MedDRA Version for Sender's diagnosis	
<b>B.5.3b Sender's diagnosis/syndrome and/or reclassification of reaction/event*</b>	

**Notes:**

Field B.3.1.c (Test name) is not indicated to be a MedDRA field at this time, though MedDRA seems to be acceptable (field allows for a 100 character alphanumeric entry).

Fields marked with \* can be LLT or PT, depending on the destination of the message; for EU regulators it is LLT, for FDA and MHLW it is PT.



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### 5 Modifiers That Change the Meaning of a Base Term

Some potential modifiers would not alter the base term's meaning, and a reclassification (e.g., change in primary SOC allocation) for the combination term would not be needed. An example of such a modifier is "acute." Other potential modifiers of this type are:

Chronic; subacute; aggravated/worsened/exacerbated; mild; moderate; severe; progressive/progression of; recurrent/relapse; intermittent; asymptomatic; no personal history of; no family history of; frequent; rare/occasional; senile/elderly; juvenile/paediatric; perinatal/neonatal; CTCAE Grades 1 – 4 (vX.X; unilateral; bilateral; left; right; upper; lower; multiple; acquired; preoperative; primary/idiopathic; secondary.

Other potential modifiers would change the meaning of the base term to such a degree that reclassification would be needed for the combination term based on MedDRA's current structure and rules. An example of this would be the potential modifier "congenital." According to MedDRA rules, any term that expresses a congenital concept has as its primary SOC allocation SOC *Congenital, familial and genetic disorders*. Other potential modifiers that would lead to reclassification are:

Familial; hereditary; postoperative/postprocedural, intraoperative; preoperative/ preprocedural; prophylaxis of.

There are a few possible ways to deal with the altered meaning of modified combination terms:

- 1) Limit the scope of potential modifiers to only those that do not change the base term meaning. On the positive side, this requires less restructuring of "new MedDRA." On the negative side, this limits the growth, and possibly the utility, of MedDRA modifiers
- 2) Eliminate primary SOC allocation rules for base terms and allow for post-modified "assignment" of SOCs by users; this has the potential of significantly altering MedDRA and changing the way that data is summarized and also allows for non-standardized usage of the terminology
- 3) "Partitioning" of modifiers. Such an approach allows for the use of a subset of modifiers for certain specific E2B fields where such terms have relevance and where potential SOC reallocations would be less significant. For example, the modifier phrase "no personal history of" is relevant only for the medical history field (B.1.7.1), while the modifier phrase "prophylaxis of" has relevance only to the indication fields (e.g., B.1.8f.2 ). "Decreased," "increased," etc. may only be applicable to SOC



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*Investigations* terms. Should there be issues related to E2B structure and format that would preclude a system approach to partitioning, an alternative would be to address this approach via the “*MedDRA Term Selection: Points to Consider*” document.



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## 6 Approach to Handle Existing MedDRA Terms with Modifiers

One of the more obvious questions in implementing modifiers is what to do with the existing terms in MedDRA that currently include modifier words or phrases. The following table provides a partial listing of potential modifiers and the number of LLTs and PTs with modifiers included in MedDRA currently (as of MedDRA 7.0).

**Table 5**

Term	LLTs	PTs	Total Terms
aggravated	299	2	301
exacerbated	18	3	21
worsening	5	0	5
relapse	7	1	8
progressive	41	14	55
progression	6	5	11
mild	23	1	24
moderate	89	1	90
severe	50	4	54
prolonged	153	21	174
recurrent	534	111	645
intermittent	15	3	18
acute	813	68	881
chronic	644	57	701
increase*	166 / 979	35 / 543	201 / 1522
decrease*	122 / 756	36 / 504	158 / 1260
<b>Total</b>	<b>2,985 / 4,432</b>	<b>362 / 1,338</b>	<b>3,347 / 5,770</b>

\* These terms reflect two totals. The first number for each term excludes the SOC *Investigations*, the second total for each term includes the SOC *Investigations*.

The conclusions that can be drawn from this subset of potential modifiers is that the number of affected MedDRA terms is significant at the LLT level (with or without SOC *Investigations* terms). The impact at the PT level is very much dependent upon the scope of the implementation. By excluding SOC *Investigations*, the impact for PTs is limited to 362 terms.

The potential implementation options include the following:

- 1) Implement modifiers to both LLT and PT levels of MedDRA in all SOC's.
- 2) Implement modifiers to both LLT and PT levels of MedDRA but exclude SOC *Investigations*.



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- 3) Implement modifiers at the PT level only in all MedDRA SOC.
- 4) Implement modifiers at the PT level only but exclude SOC *Investigations*.
- 5) Implement modifiers at the LLT level only in all MedDRA SOC.
- 6) Implement modifiers at the LLT level only but exclude SOC *Investigations*.

The following table summarizes the options described above and applies the numbers of affected terms from Table 5.

**Table 6**

Option #	Implement Modifiers with LLTs	Implement Modifiers with PTs	Implement with all SOCs	Implement all SOCs except <i>Investigations</i>	Number of Affected terms from Table 5
1	Yes	Yes	Yes	No	5,770
2	Yes	Yes	No	Yes	3,347
3	No	Yes	Yes	No	1,338
4	No	Yes	No	Yes	362
5	Yes	No	Yes	No	4,432
6	Yes	No	No	Yes	2,985

Regardless of the level of implementation chosen, the question of what to do with the affected terms currently in MedDRA exists. The choices are to make all the affected terms non-current or to leave the affected terms in place. The option of making all the affected terms non-current includes the impact of demoting all affected PTs to LLTs and then making them non-current. The MSSO may need to add base MedDRA terms if such a term does not exist. For example, if the PT *Neuromuscular block prolonged* were to be demoted to a LLT and made non-current, is there an existing term without “prolonged” currently in MedDRA or would it be necessary to add such a term?

An option to consider (if the modifier concept is approved for implementation) is to have the affected MedDRA terms stay in place as either existing LLTs or PTs. This option maintains the link to existing MedDRA coded data (e.g., locked clinical trials) and allows for the optional use of modifiers by the MedDRA community. By demoting all affected PTs to non-current LLTs, it essentially requires the implementation of modifiers by all MedDRA users. However, having two potential ways to code a single verbatim (to an existing modified MedDRA



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LLT or to a “base term + modifier” combination) may be undesirable for the majority of MedDRA users.

A potential scenario for handling existing MedDRA terms that are modified can be outlined for the relatively simple example of pancreatitis terms. Some MedDRA version 7.0 “pancreatitis” PTs with existing modifiers are PT *Pancreatitis*, PT *Pancreatitis acute*, PT *Pancreatitis chronic*, and PT *Pancreatitis relapsing*. In “new MedDRA,” only one corresponding base term, namely, *Pancreatitis*, would remain at the PT level. All of the currently modified “pancreatitis” PTs (e.g., PT *Pancreatitis acute*, PT *Pancreatitis chronic*, etc.) would be demoted to LLTs and likely made non-current along with their identical LLTs and corresponding lexical variant LLTs. All of the remaining LLTs once linked to the demoted PTs would be re-aligned to the base term PT *Pancreatitis*. To represent the concept of acute steroid-induced pancreatitis, one would select the base LLT *Pancreatitis steroid-induced* and apply the modifier “acute” to both the LLT and to the PT *Pancreatitis*.

**Table 7**

Current MedDRA	“New MedDRA”
PT Pancreatitis	PT Pancreatitis
LLT Mass forming pancreatitis	LLT Mass forming pancreatitis
LLT Pancreatitis	LLT Pancreatitis
LLT Pancreatitis aggravated	<b><i>LLT Pancreatitis aggravated*</i></b>
LLT Pancreatitis NOS	<b><i>(Pancreatitis + aggravated/worsened</i></b>
LLT Pancreatitis steroid-induced	<b><i>/exacerbated)</i></b>
PT Pancreatitis acute	LLT Pancreatitis NOS
LLT Acute pancreatitis	LLT Pancreatitis steroid-induced
LLT Pancreatitis acute	<b><i>LLT Acute pancreatitis</i></b>
LLT Pancreatitis acute on chronic	<b><i>(Pancreatitis + acute)</i></b>
PT Pancreatitis chronic	<b><i>LLT Pancreatitis acute</i></b>
LLT Chronic pancreatitis	<b><i>(Pncreatitis + acute)</i></b>
LLT Pancreatitis chronic	<b><i>LLT Pancreatitis acute on chronic</i></b>
PT Pancreatitis relapsing	<b><i>(Pancreatitis + acute + chronic)</i></b>
LLT Pancreatitis relapsing	<b><i>LLT Chronic pancreatitis</i></b>
	<b><i>(Pancreatitis + chronic)</i></b>
	<b><i>LLT Pancreatitis chronic</i></b>
	<b><i>(Pancreatitis + chronic)</i></b>
	<b><i>LLT Pancreatitis relapsing</i></b>
	<b><i>(Pancreatitis + recurrent/relapse)</i></b>
	[*LLTs in <b><i>bold italics</i></b> are likely to be non-current in “new MedDRA;” the corresponding “base term + modifier” is listed below the term]



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The scope or extent of implementation is another decision to be made. Upon review of the potential modifiers and their impact on MedDRA and MedDRA-coded data, it may be decided that the implementation be limited to a set of specific modifiers, or a specific level of MedDRA (e.g., LLT or PT) or possibly for specific purposes within the E2B message (e.g., for adverse events and indications). See also section 5 for further discussion of this idea.



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## 7 Impact of Modifiers on Hierarchy

Another aspect of the modifier issue that needs to be considered is the potential impact on the rest of the hierarchy of MedDRA, particularly, the HLG and HLT levels; it is assumed that, should the general hierarchical structure of MedDRA remain intact, that modifiers would be applied only to the non-grouping terms in MedDRA, namely, the LLT and/or PT levels. Nonetheless, there is potential for a “base term + modifier” to resemble or completely reproduce terms above the PT level. To avoid confusion and code numbering issues, such terms would need to be identified and dealt with.

In order to determine the scope of the potential impact, HLTs and HLGs in MedDRA v7.0 were searched for terms containing some potential modifiers. The results are presented in Table 8.

**Table 8**

Modifier	HLGs affected	HLT affected
Acute	0	8 Acute and chronic pancreatitis Acute and chronic sarcoidosis Acute and chronic thyroiditis Acute polyneuropathies Leukaemias acute lymphocytic Leukaemias acute myeloid Leukaemias acute NEC Multiple sclerosis acute and progressive
Chronic	0	9 Acute and chronic pancreatitis Acute and chronic sarcoidosis Acute and chronic thyroiditis Anaemias due to chronic disorders Chronic polyneuropathies Leukaemias chronic lymphocytic Leukaemias chronic myeloid Leukaemias chronic NEC Leukaemias chronic T-cell
Increased/elevated/ raised	Increased intracranial pressure and hydrocephalus	10 Calcium increased disorders Fluid intake increased Fluoride increased Increased intracranial pressure disorders Increased physical activity levels Menstruation with increased



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Modifier	HLGTs affected	HLTs affected
		bleeding Total fluid volume increased Elevated cholesterol Elevated cholesterol with elevated triglycerides Elevated triglycerides
Decreased/lowered	Decreased and nonspecific blood pressure disorders and shock	Calcium decreased disorders Decreased physical activity levels Fluid intake decreased Menstruation with decreased bleeding Total fluid volume decreased
Abnormal	Chromosomal abnormalities and abnormal gene carriers	Abnormal behaviour NEC Abnormal food elimination Abnormal gene carriers Abnormal reflexes Abnormal sleep-related events Conditions associated with abnormal gas exchange Healing abnormal NEC Red blood cell abnormal findings NEC White blood cell abnormal findings NEC
Normal		Normal newborn status Normal pregnancy, labour and delivery
Multiple		Multiple cardiac abnormalities congenital Multiple endocrine neoplasia syndromes Multiple endocrine neoplasias Multiple myelomas Multiple pregnancies Multiple sclerosis acute and progressive
Recurrent/relapse		Non-Hodgkin's lymphomas transformed recurrent
Neonatal	Foetal and neonatal investigations Neonatal and perinatal	Congenital neonatal infections Foetal and neonatal diagnostic procedures



# DRAFT

Modifier	HLGTs affected	HLTs affected
	conditions Neonatal respiratory disorders	Foetal and neonatal histopathology procedures Foetal and neonatal imaging procedures Neonatal blood incompatibility disorders Neonatal cardiovascular disorders (excl cardiorespiratory arrest) Neonatal complications of maternal substance abuse Neonatal disorders due to birth trauma (excl intracranial haemorrhages) Neonatal gastrointestinal disorders Neonatal haematologic disorders (excl blood incompatibility) Neonatal hepatobiliary disorders Neonatal hypoxia and asphyxia Neonatal hypoxic conditions Neonatal infections (excl congenital infections) Neonatal intracranial haemorrhage Neonatal metabolic and endocrine disorders Neonatal neurological system disorders NEC Neonatal respiratory arrest and failure Neonatal respiratory disorders NEC Neonatal respiratory distress related conditions Respiratory failures (excl neonatal)
Perinatal	Neonatal and perinatal conditions	0
Acquired	0	3 Acquired immunodeficiency syndromes Colour blindness (incl acquired) Vascular malformations and acquired anomalies
Primary	0	3 Extragonadal primary germ cell neoplasms



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Modifier	HLGTs affected	HLTs affected
		Primary immunodeficiency syndromes Primary mediastinal large B-cell lymphomas
Secondary	0	2 Endocrine and metabolic secondary hypertension Secondary thrombocythaemias
Progressive/progression of	0	1 Multiple sclerosis acute and progressive

It should be noted that the MedDRA SOC in version 7.0 are largely unaffected by candidate modifiers. Only SOC *Congenital, familial and genetic disorders* and SOC *Pregnancy, puerperium and perinatal conditions* contain a candidate modifier term (“congenital” and “perinatal,” respectively).

In some cases, the candidate modifier is an inherent part of the concept and should not only remain but be unaffected by the changes to the base terms linked to it (e.g., HLT *Multiple sclerosis acute and progressive*).

From a purely medical point of view, “congenital” could also be considered a candidate modifier term. This needs to be carefully considered because this one candidate modifier is highly represented at all levels of the hierarchy. In fact, for MedDRA version 7.0, the number of terms containing “congenital” per hierarchical level is as follows:

**Table 9**

Hierarchical Level	No. of “congenital” terms
SOC	1
HLGT	28
HLT	121
PT	274
LLT*	866
All levels	<b>1290</b>

\* Includes non-current LLTs



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The sizable number of LLTs and PTs involved does not preclude a reorganization step for all “congenital” terms at these levels, however, the effort to do so must be understood and weighed against the benefits (increased coding flexibility and decreased MedDRA maintenance) of leaving these as base terms within MedDRA.

In summary, with exception of the candidate modifier “congenital,” modifiers are infrequently encountered at the HLT, HLG, and SOC levels; naming conflicts should be relatively easy to address. The subscriber community will have to weigh the benefits of making “congenital” a modifier against the level of effort required to do so, but the MSSO favors making it a modifier for the tremendous flexibility such a move would provide to the user community.



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## 8 Conversion Approach

This section of the document focuses on the topic of existing MedDRA-coded data and the approaches for converting this data to a version of MedDRA that includes modifiers. This topic is an issue regardless of the level or number of modifiers applied. In order to address this topic, some assumptions must first be made. The first assumption is that the most fundamental, unmodified terms in MedDRA would not change and would remain as the base terms in new MedDRA. Examples of such terms include *Lactic acidosis*, *Polyglandular disorder*, *Cullen's sign*, *MELAS syndrome*, *Conjoined twins*, etc. These terms could be used with modifiers or without modifiers. Thus, unmodified verbatim terms could be matched (with autoencoding support for some users) to these base terms in MedDRA without the need for re-coding for the most part. For verbatim terms that contain modified concepts that correspond to current "modified" MedDRA terms (e.g., some "aggravated" concepts), these, too, may be relatively easily systematically mapped to "base term + modifiers" in "new MedDRA."

More challenging is the approach to verbatim terms that include modified concepts but which have been "best fit" to current, unmodified MedDRA terms. Schematically, the conversion paradigm works out as illustrated in Table 10 below:

**Table 10**

<b>Verbatim</b>	<b>Current MedDRA term assignment</b>	<b>MedDRA base term and modifier term assignment</b>
<b>Simple</b> Groups of pustules on scalp	<b>Simple</b> Pustule	<b>Base term</b> Pustule
<b>Modified</b> Abnormal pap smear	<b>Modified</b> Smear cervix abnormal	<b>Base term + modifier(s)</b> Pap smear + abnormal
<b>Modified</b> Possible pleural effusion right	<b>Simple</b> Pleural effusion	<b>Base term + modifier(s)</b> Pleural effusion + possible + right

The goal of this process is to update the existing MedDRA-coded data to use modifiers (when appropriate) so that any new data that will use MedDRA modifiers can be combined with existing data and subsequently extracted in an accurate and meaningful manner. The mapping process will vary a great deal based on the level or degree of modifiers implemented (see section 6 for more



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detail) as well as the terms used within each database. The impact will also be lessened if an organization has implemented a synonym list. The synonym list can be updated, and the linked data can be efficiently updated.

The MSSO could aid the conversion process by identifying all existing MedDRA terms that could potentially be affected by the implementation of modifiers. For example, the MSSO could provide a list of MedDRA terms that includes the implemented modifiers (see Table 11a below).

**Table 11a**

Verbatim	Current MedDRA Term	Current MedDRA Code	MedDRA Base Term	MedDRA Base Term Code	Modifier term	Modifier MedDRA Code
Acute tonsillitis	Acute tonsillitis	10001093	Tonsillitis	10044008	Acute	10010101

Conversion of existing MedDRA-coded data to include modifiers could be accomplished with a process outlined below:

**Step 1** – Identify dataset to be converted. Each record must include the original verbatim/as reported term, the valid MedDRA terms (three leftmost columns in Table 11a).

**Step 2** – Search the dataset for matches on affected MedDRA terms. For example, if the dataset being searched had any terms coded to *Acute tonsillitis*, the MedDRA term and code assignments could then be updated with the “new MedDRA” base term and modifier code. This also assumes that the software system/database has been modified to support modifiers.

**Step 3** – The first two steps update MedDRA term assignments for MedDRA terms that include modifiers. Step 3 searches the verbatim of each dataset term to see if a modifier is included. In the example table below, if “worsened” were identified as a modifier and the dataset had a verbatim “Halitosis worsened,” this would identify a record that could be re-coded using a modifier. This example points out one of the strengths of the modifier concept, that is, in cases where MedDRA did not support the level of detail of the verbatim, the “lost” information is regained.



**Table 11b**

Verbatim	Current MedDRA Term	Current MedDRA Code	MedDRA Base Term	MedDRA Base Term Code	Modifier term	Modifier MedDRA Code
Halitosis worsened	Halitosis	10019058	Halitosis	10019058	Worsened	10010102

It is understood that not all of the verbatim terms will make this type of direct match (e.g., the modifier “worsened” was a direct match in the verbatim “halitosis worsened.” It is possible that there are other similar verbatim terms (e.g., “halitosis made worse,” “increased bad breath”) that may also be considered. The user could either review all of the verbatim terms mapped to *Halitosis* since at least one of the verbatim terms was identified by the search for “worsened” or a capable autoencoder could be applied that could make the link and identify the verbatim terms like “halitosis made worse.”

This step also addresses an issue in the ICH “*MedDRA Term Selection: Points to Consider*” (PTC) document where modifier terms are discussed. The following text was extracted from the current version of this document (Release 3.2 Based on MedDRA version 6.1):

**3.7 Pre-existing medical conditions**

Pre-existing medical conditions that have not changed should generally be classified as medical and/or social history (See section 3.18). Pre-existing medical conditions that have changed can be classified as ADR/AEs.

- 3.7.1 It is important to capture the concept that a pre-existing condition was modified, such as aggravated, exacerbated, worsened, intermittent, recurrent, progressive, or improved. If a pre-existing medical condition is modified, the specific MedDRA term should be selected, provided that it exists.

*Example: If “exacerbation of myasthenia gravis” is reported, “Myasthenia gravis aggravated” can be selected*

- 3.7.2 In the absence of such a term, the following options are considered appropriate:

- 3.7.2.1 A term for the condition should be selected and the modification should be captured in a consistent, documented way. The non-specific modifier term alone should not be selected.

*Example: If “halitosis worsened” is reported, “Halitosis” only can be selected*



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3.7.2.2 A term for the condition and an additional term to describe the modification of the condition should be selected, e.g. “*Condition aggravated*” “*Disease progression*”

Example: If “*progression of Alzheimer’s disease*” is reported, “*Alzheimer’s disease*” and “*Disease progression*” can be selected.

Example: If “*aggravation of jaundice*” is reported, “*Jaundice*” and “*Condition aggravated*” can be selected

3.7.2.3 A new term can be requested from the MSSO. In general, the MSSO will add such terms if medical significance has been demonstrated (Introductory Guide, MedDRA Version 6.1).

The introduction of modifiers removes the need to code to a more general term (see Section 3.7.2.1 from the PTC document above) as well as use of the term *Condition aggravated* (see Section 3.7.2.2 from the PTC document above) in coding a case since, for many systems today, it is difficult to link the aggravation to a specific coded event in the case.



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### 9 Impact on Data Analysis

The least impact on data analysis would occur if the number and scope of modifiers is small and restricted to those that do not fundamentally alter the meaning of the base term; in this scenario, the current organization of MedDRA into increasingly more inclusive groupings as one ascends the hierarchy is retained. Excluded from potential modifiers would be terms that do alter the meaning of the base term and its potential SOC linkage based on current MedDRA rules; therefore, “congenital” could not fit into this design.

Greater impact on analysis would be felt if the range of modifiers is large and consists of terms that alter the meaning of a base term such that the primary SOC linkage is changed, based on current MedDRA rules. In this scenario, only the base terms could have an “assignment” to a primary and secondary SOC; application of a modifier (e.g., “congenital”) could negate any base term’s linkage to its primary SOC. MedDRA primary SOC allocations, especially the “rules” of primacy of three SOCs (*Congenital, familial and genetic disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps), and Infections and infestations*) may have to be abandoned. If this were the case, other methods of logically grouping terms in various hierarchies to facilitate analysis would have to be devised.

Using a few examples, one could foresee tabular output of modified MedDRA terms in this way:



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Table 12

MedDRA Term	Modifier	No. of cases
<b>SOC Skin and subcutaneous tissue disorders</b>	----	<b>22</b>
HLT Hypopigmentation disorders	----	19
PT Skin depigmentation	Aggravated/worsened/ exacerbated	12
PT Vitiligo	----	5
PT Vitiligo	Chronic	2
<b>SOC Vascular disorders</b>	----	<b>13</b>
HLT Vasculitides NEC	----	12
PT Thromboangiitis obliterans	----	2
PT Vasculitis	----	7
PT Vasculitis	Diffuse	2
PT Vasculitis	Diffuse + chronic	1

Another essential aspect of data analysis using MedDRA-coded data that needs to be considered is the generation of queries, i.e., lists of MedDRA terms to identify and aggregate cases based on a condition of interest. In “new MedDRA,” it is predicted that PTs may function more along the lines of grouping terms (i.e., like HLTs and HLGs) as illustrated by the “pancreatitis” example discussed in section 5. One could most likely still base queries on PTs or higher terms and still retain the ability to capture cases related to the topic of interest, irrespective of the application of modifiers. For certain, highly specific queries (e.g., looking *only* for acute pancreatitis cases), one may need to search for terms that have the appropriate modifier, but it is assumed that a well-designed database would be able to perform this function systematically.



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### 10 Recommendations

As with many new initiatives, the number of questions raised by the modifier concept may seem daunting and could discourage implementation. The MSSO believes the concept merits additional discussion with all stakeholders so more complete understanding of the benefits and impacts can be considered before a final decision is made. As a starting point for the discussion, the MSSO proposes the following as initial steps to support a decision:

1. An initial set of modifiers (i.e., acute, chronic, subacute, aggravated/worsened/exacerbated, progressive/progression of, recurrent/relapse, intermittent, and grade 1 - 4 CTCAE (version X.X)) will be considered for implementation. This initial set of modifiers is a subset of the modifiers identified in the Appendix. If this initial set of modifiers is implemented and found to be useful, other modifiers could be considered for implementation. In the long term, MedDRA subscribers could expand the list through a change request process.
2. The E2B message format should be modified to support modifiers. This will include adding a repeatable block to each existing MedDRA term in the current E2B message.
3. The implementation timeline should be significant (12-18 months) to allow users and software vendors time to make the necessary changes to systems to incorporate modifiers as well as preparing existing coded databases for the transition to a version of MedDRA with modifiers.
4. The ICH "*MedDRA Term Selection: Points to Consider*" document would need to be revised to not only accommodate the modifier concept (e.g., current Section 3.7 of PTC document) but also to provide guidance on the proper use of modifiers (e.g., what modifiers should be used for medical history terms vs. adverse event terms).
5. The MSSO should facilitate discussions with all stakeholders (i.e., regulators, industry, system developers, academia) and ICH working groups (e.g., PTC, E2B) to encourage dialogue on the topic from all affected groups. One of the initial steps for facilitation planned by the MSSO is a Blue Ribbon Panel (BRP) meeting (schedule for 18 June 2004) made up of MedDRA and E2B experts from the three ICH regions to provide their views on the modifiers concept.
6. The MSSO will collect feedback from stakeholders and present the results to the MedDRA Management Board for consideration.



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**Appendix — List of Potential Modifiers**



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## Potential Modifiers

A MedDRA modifier is a word or phrase that can be applied to another MedDRA term to modify its basic meaning. Based on the nature of additional meaning that a modifier adds to the original concept and the impact on MedDRA's current structure, modifiers can be grouped as follows:

1. Modifiers that do not change significantly the meaning of the base term, which means it does not alter the primary SOC in terms of the way MedDRA is currently organized (this group has relatively little impact on data retrieval or analysis):

Group I: modifiers for disease progression regarding time or pathology

1. acute
2. chronic
3. subacute
4. aggravated/worsened/exacerbated
5. mild
6. moderate
7. severe
8. progressive/progression of
9. recurrent/relapse
10. intermittent
11. asymptomatic
12. no personal history of
13. no family history of
14. frequent
15. rare/occasional
16. senile/elderly
17. juvenile/paediatric
18. perinatal/neonatal
19. acquired
20. CTCAE Grade 1 (version X.X)
21. CTCAE Grade 2 (version X.X)
22. CTCAE Grade 3 (version X.X)
23. CTCAE Grade 4 (version X.X)

Group II: modifiers for disease etiology

24. primary/idiopathic
25. secondary

Group III: modifiers for anatomical locations

26. unilateral
27. bilateral
28. left
29. right



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30. upper
31. lower
32. multiple

2. Modifiers that change the original concept leading to a different primary SOC allocation based on current MedDRA rules  
(a relationship between this type of modifier and a new primary SOC may need to be established):

33. prophylaxis of
34. postoperative/postprocedural
35. intraoperative
36. preoperative/preprocedural
37. congenital
38. familial
39. hereditary

3. SOC *Investigation* terms

40. increased/elevated/raised
41. decreased/lowered
42. normal
43. abnormal
44. positive
45. negative
46. prolonged (investigation)
47. shortened (investigation)