CTCAE version 3
Vocabulary Standards Review
“Review of the Review”

Presented by

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Based on work by Jim Cimino and the CTCAE Review Team (circa 2007)
Note: The evaluation of the CTCAE (Common Terminology for Adverse Events) version 3.0 was performed late 2006 and presented to the caBIG Workspace in January and April 2007. This is a summary of that review performed by Jim Cimino and the CTCAE review team. Much of the following information is derived from that report and the source documents can be referenced from Vocabulary Standardization section of GForge.
• The “native” version of CTCAE version 3.0 was available as a text document encoded in PDF and browsers/coders
• No clear delineation of “terms”
  • No term identifiers
  • Adverse Events (AEs):
    • terms in their own right?
    • only when postcoordinated with grades?
• Are there 5 grades or ~ 5000?
  • Grades definitions (within the same grade) are inherently unique due to contextual dependency on the AE term
• Therefore, no “Finite, enumerated set of terms to convey information unambiguously”
• Evaluation using standard criteria is problematic
NB: At the time of the CTCAE Review in 2006, the vocabulary standards review was in version 2.0.

Changes have been made and it is now in version 3.0 (shown to the left).
Vocabulary Review Criteria

**Structure**
The overall “data model” of the terminology

**Content**
The extent of domain coverage within the terminology as well as representation via textual definitions, use of “not elsewhere classified” (NEC) terms, polyhierarchy, formalism regarding concept usage, etc.

**Documentation**
Purpose and scope; statement of intended use; description of usage of codes/identifiers, output formats, use of semantic relationships; tooling available, etc.

**Editorial Process**
Curation process; concept permanence; QA and QC; extensions to other terminologies, etc.
CTCAE v3.0 was *reified* for representation within the NCI Thesaurus

Three approaches were considered…

1. AEs are terms, 5 Grades are modifiers
   Link AEs to allowable Grades
   Most compact form
   Loses context-specific meanings of Grades

2. AEs are terms, AE-specific Grades are terms
   Link through “has-grade” relationships
   Allows reuse of Grades
   Useful with Supra-Ordinate groups
   Care must be exercised (Death=Death?)

3. **Precoordinate AEs and allowable Grades**
   Simplifies relationships to “is-a”
   Largest possible version
   No re-use, but reduces redundancy/ambiguity
NCIt Reification

1. Concept is unit of discourse
2. Concepts have unique identifiers
3. Terms are from sources, mapped to concepts
4. Information available in various file formats
5. CTCAE has been incorporated into NCIT
6. Precoordination approach taken
7. NCIT Flat File, XML and OWL versions

NCIT Flat File
C57213|CTCAE_Grade_1_Nausea| Nausea_Adverse_Event| Nausea
CTCAE Grade 1 Nausea| Grade 1 Nausea

NCIT XML

```xml
<conceptDef>
  <name>CTCAE_Grade_1_Nausea</name>
  <code>C57213</code>
  <id>57213</id>
  <namespace>NCI</namespace>
  <kind>Findings_and_Disorders.Kind</kind>
  <definingConcepts>
    <concept>Nausea_Adverse_Event</concept>
  </definingConcepts>
  <definingRoles/>
  <properties>
    <property>
      <name>Preferred_Name</name>
      <value>CTCAE Grade 1 Nausea</value>
    </property>
    <property>
      <name>Semantic_Type</name>
      <value>Finding</value>
    </property>
    <property>
      <name>Synonym</name>
      <value>CTCAE Grade 1 Nausea</value>
    </property>
    <property>
      <name>Synonym</name>
      <value>Grade 1 Nausea</value>
    </property>
  </properties>
</conceptDef>
```
CTCAE in NCIt

- Naming conventions
  - Categories: “Adverse Event Associated with X”
  - Supra-Ordinates: “X Adverse Event”
  - AEs: “X Adverse Event”
  - Grades: “CTCAE Grade n X”

- Stats
  - 28 Categories
  - 5 Grade terms
  - 51 Supra-Ordinate terms
  - 1,043 Aes
  - 4,472 AE-Grade pre-coordinations

- Included content
  - Codes
  - Semantic types (all are “Finding”)
  - Labels and Preferred Names
  - Subclass_of
  - Synonyms and Definitions
Therefore, there were *two* instances of the terminology…

- Native CTCAE version as a text document
- NCIt version

The review uniquely performed the evaluation of *both* in parallel. This comparison is an important outcome of that review and the basis of comparative recommendations made.

These recommendations remain important to the evolution to version 4.0, although some may be less relevant or perhaps even obsolete given recent goals or objectives in the design of the next version.
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
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<th>E</th>
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<th>I</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Evaluation of CTCAE Using Revised Vocabulary Review Criteria – VRC version 2.0</td>
<td>Vocabulary Assessment</td>
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<td>2</td>
<td>Understandability, Reproducibility and Utility (URU) – Does the vocabulary conform to the highest degree practicable to the standards of good vocabulary practices laid out by the community?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See CTEP publications&lt;/ref&gt;</td>
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<tr>
<td>3</td>
<td>Vocabulary purpose and scope</td>
<td>Is the purpose and scope of the vocabulary clearly stated in operational terms so that its fitness for particular purpose can be assessed and evaluated?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td></td>
<td>Reasonable domain coverage; NEC terms cover gaps; but no formal evaluations available</td>
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<tr>
<td>4</td>
<td>Vocabulary content coverage</td>
<td>Does the vocabulary provide comprehensive or explicit in-depth coverage of the domain of interest it claims to address as stated in purpose and scope of the vocabulary element?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>CTEP has no plans to modify CTCAE; NCIT would encompass changes if they occurred. &lt;ref class=&quot;text&quot;&gt;See 5&lt;/ref&gt;</td>
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<tr>
<td>5</td>
<td>Are there explicit, reproducible methods for recognizing and filling gaps in the vocabulary?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<tr>
<td>6</td>
<td>Vocabulary concept orientation</td>
<td>Does each concept have a single, coherent meaning?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<td>7</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
<td>Does the vocabulary support synonyms and is vocabulary explicitly connected?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>Available in published and electronic formats</td>
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<td>8</td>
<td>Are relationships between concepts uniform within the vocabulary structure?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>NCIT has logical representation; CTEP does not</td>
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<td>9</td>
<td>Concept permanence</td>
<td>Is the meaning of a concept, once created, immutable?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<td>10</td>
<td>Semantical concept identifiers</td>
<td>Does each concept have a unique identifier?</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<td>11</td>
<td>Are concepts free of hierarchical or other implicit meaning?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<td>12</td>
<td>Are identifiers NOT re-used when a concept is made obsolete or is suppressed?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See BJ&lt;/ref&gt;</td>
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<td>13</td>
<td>Hierarchical organization</td>
<td>Is the basic principle for any hierarchical arrangement explicitly stated?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>Published version has no hierarchy; NCIT uses subclass of relationship. Published version has no hierarchy; NCIT can support polyhierarchy but uses it sparsely. &lt;ref class=&quot;text&quot;&gt;See 17J&lt;/ref&gt;</td>
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<td>14</td>
<td>Is the vocabulary organized as a polyhierarchy?</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See 17J&lt;/ref&gt;</td>
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<td>15</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
<td>Are concepts capable of having multiple meanings in the case of a polyhierarchy?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See 17J&lt;/ref&gt;</td>
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<td>16</td>
<td>Formal definitions</td>
<td>Does each term have a definitive set of relationships to other concepts that, taken together, are both individually necessary and collectively sufficient to distinguish the concept from all other concepts?</td>
<td>&lt;ref class=&quot;text&quot;&gt;CTEP, NCIT&lt;/ref&gt;</td>
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<td>No semantic relations except hierarchy</td>
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<td>Does the vocabulary make explicit which concepts are atomic (i.e. non-composite)?</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See 20J&lt;/ref&gt;</td>
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<td>18</td>
<td>Does the vocabulary support the creation of composite concepts?</td>
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<td>&lt;ref class=&quot;text&quot;&gt;See 20J&lt;/ref&gt;</td>
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<td>Purpose and Scope</td>
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<td>Vocabulary Content Coverage</td>
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<td>Concept Orientation</td>
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<td>Concept Permanence</td>
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<td>Nonsemantic Concept Identifier</td>
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<td>Polyhierarchy</td>
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<td>Formal Definition</td>
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<td>Explicitness of Relations</td>
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<td>Rejection of NEC</td>
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<td>Multiple Granularities</td>
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<td>Multiple Consistent Views</td>
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<td>Context Representation</td>
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<td>Graceful Evolution</td>
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<td>Recognize Redundancy</td>
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</table>
1. Describe the essential nature of the concept – Yes
2. Concise, precise and unambiguous – Generally Yes
3. However, some parts of definitions may themselves be ambiguous. For example, although used frequently, "major urgent intervention" is not explicitly described. So, for example, would biliary tree hemorrhage requiring transfusion of 10 units of blood be considered Grade 3 ("Transfusion, interventional radiology, endoscopic, or operative intervention indicated") or 4 ("major urgent intervention indicated")?
4. Avoidance of rationale, functional usage or procedural information - Yes
5. Consistent terminology and logical structure – Yes
6. Description logic relationships to other terms in the terminology – No
## Review Summary

### Evaluation of CTCAE Using Revised Vocabulary Review Criteria -- VRC version 2.0

<table>
<thead>
<tr>
<th></th>
<th>Vocabulary Assessment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>meets criterion</td>
<td>partially meets criterion</td>
<td>does not meet criterion</td>
<td>criterion not applicable</td>
<td>criterion not assessed</td>
</tr>
<tr>
<td>CTEP</td>
<td>26</td>
<td>14</td>
<td>54</td>
<td>4</td>
<td>1</td>
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<tr>
<td>NCIT</td>
<td>68</td>
<td>14</td>
<td>12</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Criteria met

Criteria partially met

Criteria not met

Criteria not applicable

Criteria not assessed
Summary and Conclusions (2007)

- CTCAE is not a true controlled terminology
- CTEP version of CTCAE does not meet most criteria
- NCIT succeeds in providing CTCAE as a terminology
- NCIT construction of CTCAE *meets most* criteria
  - Polyhierarchy could use work
  - NEC is not so bad (if used sparingly in practice)
  - Formal definitions, context representation, & redundancy detection hard
- Some semantics are lost
- A few inconsistencies were found
- AE-Grade names unhelpful
- Codes should be used as pointers
- Separate files would be nice
- Content maintenance is an issue
- Formal evaluations of content lacking
- Reconciliation with MedDRA is an issue