

Overview Document

CTCAE

Working Group Initial Teleconference Meeting

Rockville, MD
July 8, 2008

Agenda

- ▶ Welcome/Introduction : Frank Hartel CBIIT
- ▶ CTCAE v3.0 Background and Purpose Alice Chen, M.D CTEP
- ▶ CTCAE v3.0 Structure and Recent Review/Activities
 - MedDRA MSSO Blue Ribbon Panel Ann Setser CBIIT
 - CTEP, FDA discussions Stuart Turner
 - VCDE, caBIG review
- ▶ CTCAE v3.0 Revision Issues Ann Setser CBIIT
- ▶ CTCAE v3.0 Revision Project Governance
 - Roles & Responsibilities: Alice Chen, M.D CTEP
- ▶ CTCAE Content Revision Ann Setser CBIIT
- ▶ CTCAE v3.0 Revision Project Methods Ranjana Srivastava

CTCAE v3.0 Background and Purpose

Alice Chen, M.D., CTEP NCI

CTC / CTCAE Background and History

- ▶ The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) developed the original Common Toxicity Criteria (CTC) in 1983 to aid in the recognition and grading severity of adverse effects of chemotherapy
- ▶ A list of AE terms commonly encountered in oncology accompanied by an associated grading (severity) scale for each AE

CTC	CTC v2.0	CTCAE v3.0
1983	1998	2003
49 AE Terms	~300 AE Terms	1,059
	Appendix: Late Radiation Morbidity Scoring Scheme	Acute & Late AEs– Appendices deleted
	Appendix: BMT Complex/ Multi-component Events	All modalities Appendices deleted
	Pediatric-specific	Few Pediatric-specific
	Mapped to MedDRA (imperfect mapping)	Mapped to MedDRA (imperfect mapping)

CTCAE v3.0 Purpose in Oncology Research

- ▶ Provide a list of AE terms commonly encountered in oncology
- ▶ Assist in the recognition and severity grading of AEs
- ▶ Standardize reporting of AEs across groups and modalities without regard to chronicity
- ▶ Supply guidelines for protocol parameters:
 - Eligibility
 - Dose Limiting Toxicity
 - Maximum Tolerated Dose
 - Dose modifications
- ▶ Monitor safety data
 - Regulatory reporting
- ▶ Facilitate the evaluation of new therapies, treatment modalities, and supportive measures

CTCAE v3.0 Structure and Recent Review/Activities

Structure

Ann Setser CBIT

MedDRA MSSO Blue Ribbon Panel

Ann Setser CBIT

CTEP, FDA discussions

Ann Setser CBIT

VCDE, caBIG review

Stuart Turner UC Davis

CTCAE v3.0 Components

- ▶ Adverse Event Term
- ▶ Supra-ordinate Term
- ▶ Grading Scale
- ▶ Also Consider
- ▶ Navigation Notes
- ▶ Mapped to MedDRA LLT (imperfect)

CTCAE v3.0 Components Adverse Event Term

CARDIAC GENERAL							Page 1 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death	

REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.

Adverse Event Term

- Mapped where possible to MedDRA LLT

CTCAE v3.0 Components Supra-ordinate Terms

GASTROINTESTINAL						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Fistula, GI – Select: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – Select	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death

Supra-ordinate term

- Is a grouping term based on disease process, signs, symptoms, or diagnosis
- Is accompanied by specific AEs that are all related to the Supra-ordinate term
- Provides clustering and consistent representation of Grade (severity descriptions) for related AEs
- Are not AEs, are not mapped to a MedDRA LLT term
- Cannot be used for reporting

CTCAE v3.0 Components Adverse Event Grading Scale

CARDIAC GENERAL							Page 1 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death	

REMARK: Use age and gender-appropriate normal values; >95th percentile ULN for pediatric patients.

Grading/severity scale

- Unique for each AE term

CTCAE v3.0 General Descriptions of Grade

0	No adverse event or within normal limits
1	Mild Adverse Event (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
2	Moderate Adverse Event (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
3	Severe and undesirable Adverse Event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
4	Life-threatening or disabling Adverse Event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
5	Fatal adverse event

CTCAE and MedDRA Recent Activities

- ▶ April 2006 MedDRA MSSO Blue Ribbon Panel

- ▶ February 2008 FDA – CTEP, NCI CTCAE discussions

- ▶ June 2008 CBIIT, caBIG, VCDE CTCAE Revision Project

MedDRA MSSO Blue Ribbon Panel - April 2006

AstraZeneca	Human Genome Science, Inc
Bayer Healthcare Corporation	Johnson & Johnson
Bristol Myers Squibb	MedImmune, Inc.
Celgene Corporation	Merck and Company
Charles River Laboratories	META Solutions
Chugai Pharmaceutical Co	National Cancer Institute
Eisai Medical Research	PSI International, Inc
EMMES Corp.	Radiation Therapy Oncology Group(RTOG)
Hoffman La Roche	Schering AG, and Schering AG
AFSSAPS	FDA

MedDRA MSSO Blue Ribbon Panel

- ▶ CTCAE & MedDRA
 - MedDRA is used by the biopharmaceutical industry and regulatory agencies within the ICH regions
- ▶ CTCAE use by Industry
 - CTCAE is widely used in oncology and HIV clinical research
 - To facilitate data exchange within internal databases using MedDRA and with regulatory authorities for the purpose of SAE reporting, must establish a mechanism to ‘translate’ or ‘convert’ CTCAE terms from investigators to MedDRA terms.
 - CTCAE mapped to MedDRA
- ▶ Summary of recommendations
 - Stakeholders should dialogue to address optimal use of both terminologies
 - Other recommendations:
 - http://www.meddramsso.com/MSSOWeb/activities/archive_brp.htm

FDA, CTEP NCI

- ▶ Agreement between FDA and CTEP
 - Revise CTCAE v3.0 to become CTCAE v4.0:
 - 100% single concept MedDRA terms
 - Isolate critical concepts within Grades as unique AE terms
 - Other issues

caBIG VCDE Evaluation of CTCAE v3.0

January 2007

- ▶ Purpose: To assess the CTCAE with respect to the Vocabulary Criteria established by the VCDE to establish standards for the NCI's Cancer Biomedical Informatics Grid (caBIG)

CTCAE v3.0 Revision Issues

Ann Setser, CBIIT

CTCAE v3.0 Issues

- ▶ CTCAE v3.0 Terms
 - Multiple concepts
 - Multiple concepts in one AE Term;
Concept of AE Term is also a Grade Identifier
 - One/many element of Grade description is critical AE concept
 - Not all MedDRA terms
 - 72% CTCAE = mapped to a single MedDRA term/code (not valid 1:1 map)
 - 28% CTCAE = CTEP*-code (leading 9's with meaning only inside CTEP)

CTCAE v3.0 Multiple Concepts in one Adverse Event Term

CONSTITUTIONAL SYMPTOMS							Page 1 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—	

Mapped to MedDRA: Fatigue 10016256

Fatigue, Asthenia, Lethargy, Malaise

- Are unique concepts in MedDRA (PTs)
- Are not
 - related to a single Preferred Term
 - synonyms, lexical variants, or quasi-synonyms

CTCAE v3.0 Multiple concepts in one Adverse Event Term; Concept of AE Term is also a Grade Identifier

CARDIAC GENERAL						Page 1 of 3
Adverse Event	Short Name	Grade				
		1	2	3	4	5
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death

CTCAE v3.0 Critical concept listed in Grade only – not as Adverse Event Term

ALLERGY/IMMUNOLOGY							Page 1 of 1
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death	
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).							
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.							

CTCAE v3.0 Revision Project Governance Roles & Responsibilities

Alice Chen, CTEP NCI

CTCAE Revision Project

▶ CTCAE v4.0

- Open collaboration with broad oncology community
 - Cancer Centers, Industry, FDA, MedDRA MSSO, NCI, Others

▶ The Importance of Establishing a CTCAE Review Community

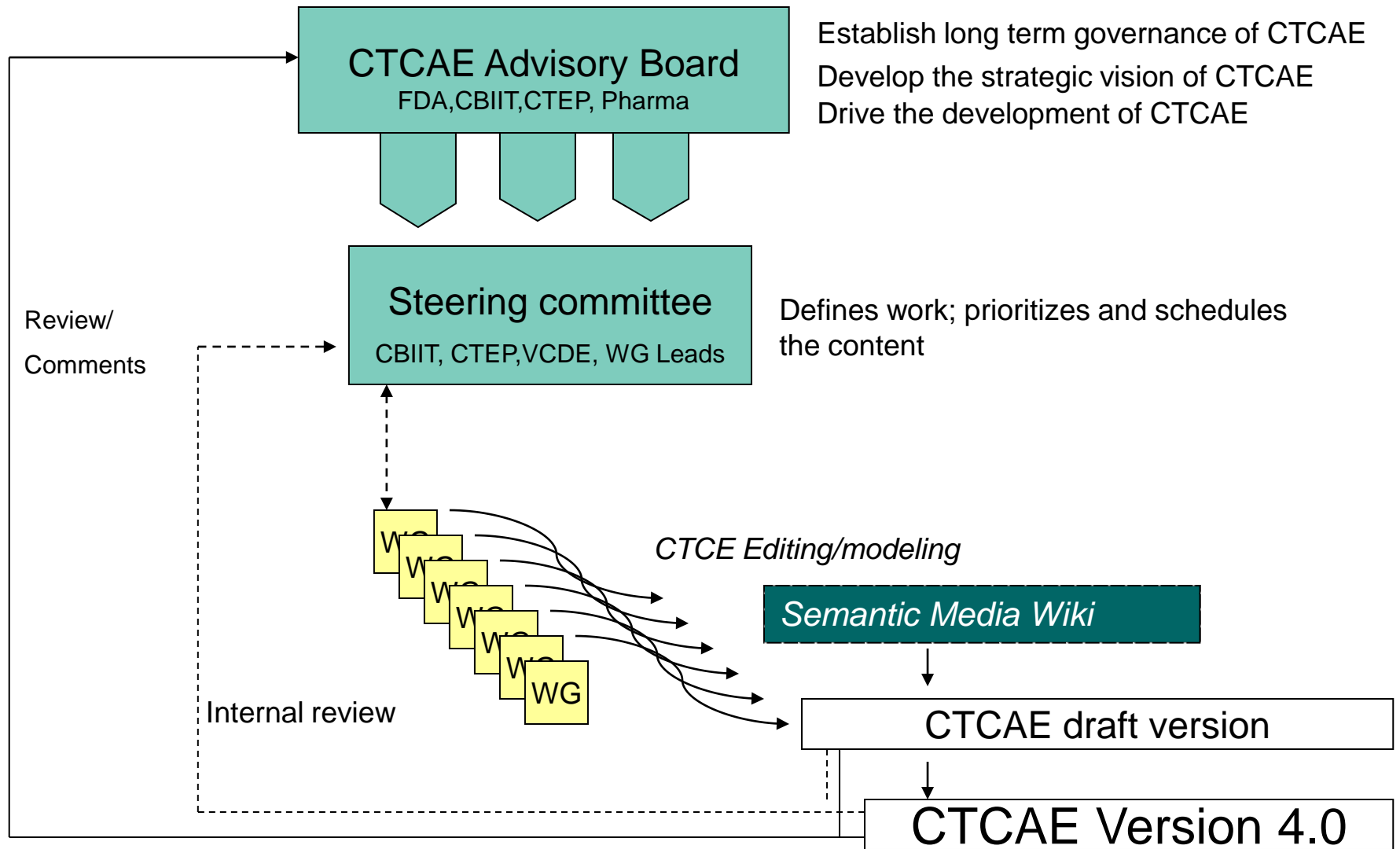
▶ To maintain the CTCAE terminology set in the long term, a life cycle management system is needed, including:

- A governance structure
- Coordinated review processes and procedures
- An active participating community of subject matter experts

▶ The CTCAE Community will be responsible for:

- Establishing long term governance of the CTCAE
- Setting general direction for the actual revision of the existing CTCAE content
- Defining the structure and process to be used during the CTCAE revision
- Assuring that the revised CTCAE is machine interpretable and follows caBIG™ terminology requirements
- Addressing the actual content revision of CTCAE

CTCAE v3.0 Revision Project: Structure



CTCAE v3.0 Revision Project: Advisory Board

- ▶ Member Composition - CBIIT, CTEP, FDA, Pharma, Investigators
- ▶ Advisory Board Chair - TBD
- ▶ Board members will serve until CTCAE v4.0 release
 - After v4.0 release revisit membership
- ▶ Establish a long term governance of the CTCAE
- ▶ Strategic vision of CTCAE in the future including revisions post version 4.0
 - Will need to develop SOPs to follow over time for the appropriate governance for subsequent revisions
- ▶ Review each Revision DRAFT Product for version 4.0

Steering Committee

- ▶ Member composition - CBIIT, CTEP, VCDE, Working Group Leads, Pharma, investigators
- ▶ Steering Committee Chairs will be Lawrence Wright, Alice Chen and Ann Setser
- ▶ Purpose – Technical and content oversight for the CTCAE Revision Project
- ▶ Responsibilities include:
 - Defining the structure and process to be used during the CTCAE revision
 - Prioritizing and scheduling of content submitted to the Working Group
 - Overseeing day-to-day activities of the Working Groups
 - Addressing cross-Working Groups issues
 - Ensuring uniformity across Working Groups
 - Providing internal review of updates
 - Ensure adherence to caBIG™ vocabulary review criteria
- ▶ Steering Committee will be expected to work virtually but also convene (via Centra session) in person as needed
- ▶ Voting structure - majority
 - A Working Group lead cannot vote on their own Working Group's products
- ▶ Steering Committee will review the drafts of the each revision

CTCAE v3.0 Revision Project Working Groups

- ▶ Working Groups are organized by MedDRA SOCs (System, Organ, Class)
 - MedDRA includes 26 SOCs
 - Highest level of the MedDRA terminology, distinguished by anatomical or physiological system, etiology, or purpose. Examples:
 - * Cardiac disorders
 - * Metabolism and nutrition disorders
 - CTCAE Revision Project includes 12 Working Groups
 - Each Working Group is assigned CTCAE v3.0 AE terms and candidate CTCAE v4.0 terms within one or more SOCs
 - Members are distributed to the Working Group based on their areas of expertise
 - SOCs are organized into working groups that may allow for cross areas of expertise among members:
 - * Working Group #2: SOC Cardiac disorders + SOC Vascular disorders
 - * Working Group #4: SOC Psychiatric disorders + SOC Nervous system disorders

Working Group Roles and Responsibilities

- ▶ WG will be provided educational material on MedDRA, Semantic Wiki
- ▶ WG will be provided with current CTCAE v3 AEs that is currently organized into their SOC to review, validate and add/delete
- ▶ Decisions will be based on majority vote
 - Voting will occur through multiple mechanisms including teleconferences, e-mail and Wiki
 - When voting takes place via teleconferences and not all members are present, the absent members will have a 3 day (weekend included) window to vote via e-mail or Wiki
 - Steering Committee will resolve any Working Group voting impasse
- ▶ Working Group Member
 - Serve until the release of CTCAE v4.0
 - Attend (at a minimum) weekly teleconference calls (~1.5 hours per call)
 - Contribute and sometimes lead the analysis of terms

Working Group Lead Roles and Responsibilities

- ▶ Working Group Lead
 - Serve as the Working Group representative on the Steering Committee, and participate in all Steering Committee activities
 - Liaise with other Working Group leads
 - Set deadlines in conjunction with NCI and the Booz Allen project team
 - Be responsible for timely completion of the assigned work
 - Update the Steering Committee on the progress of the revision process
 - Present the Working Group's recommendations to the Steering Committee
 - Resolve any Working Group issues via the Steering Committee
 - Ensure adherence to caBIG™ vocabulary review criteria
 - In addition to weekly teleconference calls as a Working Group member, he/she will be participating in the teleconference or F2F Steering Committee meetings
 - Communicate with their Working Group members decisions made in the Steering Committee

CTCAE Content Revision

Ann Setser, **CBIIT**

CTCAE Content Revision

▶ Objective for Revision v4.0 Draft 3.1

- Reconciliation with MedDRA
- Agree on a list of Adverse Event terms for assigned SOCs
- Ensure each CTCAE term is a single concept MedDRA term
- Split multiple concept CTCAE v3.0 terms
- CTCAE v4.0 AE terms (single concept MedDRA terms) will be listed by MedDRA SOC, replacing historical CTCAE 'CATEGORY'
- Identify critical concept AE terms embedded within CTCAE v3.0 GRADE Description – AE terms that should be listed as unique CTCAE v4.0 (MedDRA) terms

CTCAE Content Revision Timeline

- ▶ **Objective for Revision v4.0 DRAFT 2 [Representation of additional MedDRA AE terms and Severity Grades]**
 - Review suggested additional AE terms
 - Logged from historical use of CTCAE v3.0
 - Recommendations from v4.0 DRAFT1 work
 - Review CTCAE v3.0 Severity Grade descriptions
 - Revise CTCAE v3.0 if necessary
 - Develop Grading Scale for new AE terms listed in v4.0 DRAFT1
 - Review and revise for consistency across all AE Grades
 - Add term definitions

- ▶ **Objective for Revision v4.0 Draft 3**
 - Collate recommendations from public review of v4.0 DRAFT
 - Finalize list of AE/MedDRA terms
 - Finalize Grading Scale

Sample Tasks / Steps for Revision v4.0 DRAFT1

- ▶ Documents for WG review will include one Excel file for each current CTCAE v3.0 CATEGORY

Example: GASTROINTESTINAL

- ▶ Each file will include 6 worksheets:

<i>CATEGORY_AsIs;</i>	<i>CATEGORY_Rev;</i>	<i>SOC_Name;</i>
<i>AdEERS_CDUS_Reported;</i>	<i>AdEERS_CDUS_All_AEs;</i>	<i>Autocode</i>

- ▶ Review current CTCAE v3.0 terms: determine if split term appropriate? Additions? Deletions? Modifications? Concerns?
- ▶ Review Grading Scale for each current CTCAE v3.0 term to determine if any concept embedded within a GRADE ought to be listed separately as an AE term.
- ▶ All CTCAE v3.0 terms and revised v4.0 terms will be listed within their MedDRA SOC, replacing the historical CTCAE CATEGORY

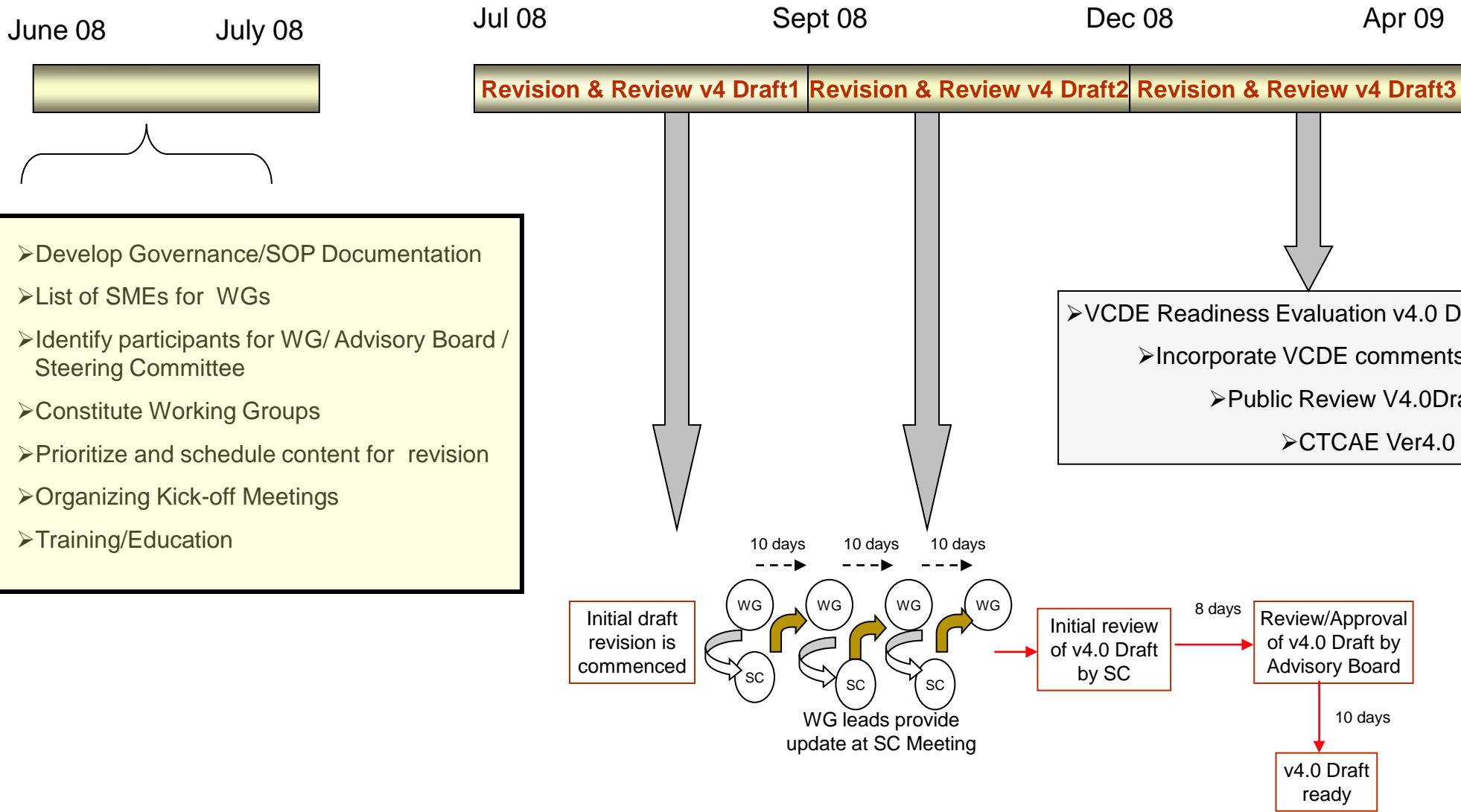
Sample Tasks / Steps for Revision v4.0 DRAFT2

- ▶ Revise Severity Grade Terms
 - Create AE Terms identified from GRADE Description in v4.0 DRAFT1
 - Provide Grading Scale
 - For the original AE term from which the GRADING concept was removed
 - For the new term/concept removed from the GRADE
- ▶ Standardize GRADE Description
 - Example: Symptomatic and interfering with ADL; **operative** intervention indicated
 - Symptomatic and interfering with ADL; **surgical** intervention indicated
 - Symptomatic interfering with ADL; **invasive** intervention indicated
- ▶ AEs reported to CTEP via AdEERS & CDUS via “Other, Specify” verbatim
- ▶ Supra-ordinate term mapping to MedDRA HLT and Select terms which may reuse a single grading scale
- ▶ AE/Grading scale recommendations from CTEP HelpDesk & use of CTCAE v3.0
- ▶ Definitions
- ▶ Synonyms: associated or substitute terms
- ▶ Other...

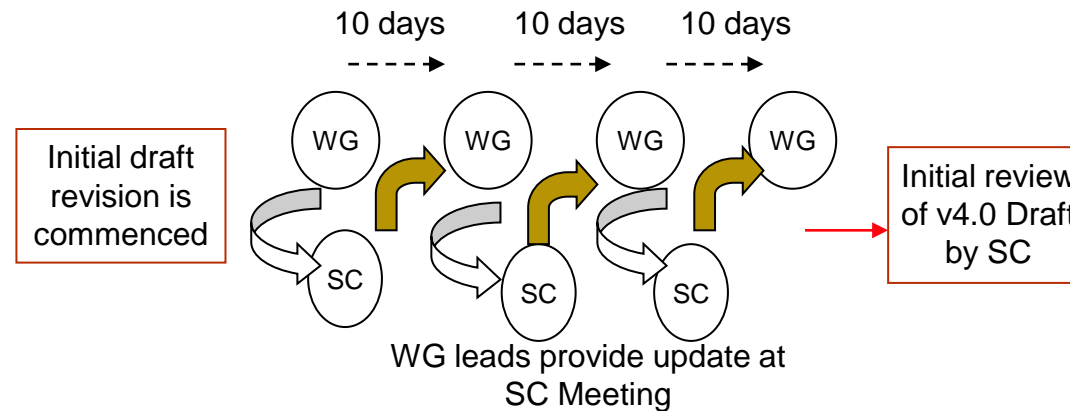
CTCAE Revision Project Timeline and Process

Ranjana Srivastava, Booz Allen Hamilton

CTCAE v3.0 Revision Project Process and Timeline



CTCAE v3.0 Revision Process



- ▶ The revision period for each draft version will be divided into three phases, each ~ten days long.
- ▶ At the end of approximate ten days, the WG Leads will meet at the SC meeting to provide an update of the revision and discuss any issues, and then communicate to their respective Working Groups, any concerns/comments.
- ▶ Following the SC meeting, each group will meet at least once, to discuss revision issues with the BAH project manager and Ann Setser from CBIIT.
- ▶ VCDE Participant from the Steering Committee will ensure the caBIG compatibility of the revised terminology.
- ▶ All meetings will be organized via Centra which can be accessed at <http://ncicb.centra.com>

CTCAE Draft v4.0 Review Process

▶ Review v4.0 Draft1 & 2

- Initial Review of each draft version by the Steering Committee
- Review and approval by Advisory Board

▶ Review v4.0 Draft 3 (final)

- Evaluation by VCDE
 - To ensure adherence to caBIG™ vocabulary review criteria
 - Incorporate VCDE comments
- Public Review v4.0 Draft 3.0
 - Terminology will be posted on the GForge site for a period of 30 days
 - Comments received will be reviewed and evaluated by the Working Group for incorporation into v4.0 followed by review and endorsement by the Advisory Board

Semantic Media Wiki

- ▶ All editing / changes to the terminology will be done using the BiomedGT Content Development Platform
- ▶ The BiomedGT is a tool for collaborative terminology authoring developed by the National Cancer Institute Center for Bioinformatics, Apelon, Inc. and the Mayo Clinic Division of Biomedical Informatics.
- ▶ All WG members will have an account on the BiomedGT
- ▶ A second all hands Working Group meeting is being scheduled to educate members on Semantic Media Wiki
- ▶ Website: <http://biomedgt.org>

Next Steps

- ▶ Schedule a second all hands Working Group meeting to educate members on:
 - MedDRA
 - Semantic Media Wiki
 - caBIG™ VCDE Review/Evaluation of CTCAE
- ▶ Schedule Steering Committee kick-off meeting
- ▶ Schedule individual Working Group meetings
- ▶ Schedule Advisory Board kick-off meeting