CTCAE 4.0

It is something of an understatement to call CTCAE 4.0 a version change. It is a complete reorganization of NCI's system of adverse event reporting. The driving force behind 4.0 was alignment of NCI's AE classifications with MedDRA, the Medical Dictionary for Regulatory Activities, an adverse event reporting standard accepted internationally by the pharmaceutical industry and governments. This change required eliminating some previously used AE terms, adding new AEs, and realignment of AEs from the long-used CTCAE *Categories* to MedDRA's *System Organ Classes* (SOCs).

This table compares the general organization of 3.0 to 4.0:

CTCAE v3.0 CATEGORY	Count	CTCAE v4.0 SOC	Count
ALLERGY/IMMUNOLOGY	6	Immune system disorders	6
AUDITORY/EAR	6	Ear and labyrinth disorders	9
CARDIAC ARRHYTHMIA	32	Cardiac disorders	36
CARDIAC GENERAL	16		
CONSTITUTIONAL SYMPTOMS	11	General disorders and administration site conditions	24
DERMATOLOGY/SKIN	28	Skin and subcutaneous tissue disorders	34
ENDOCRINE	15	Endocrine disorders	11
GASTROINTESTINAL	140	Gastrointestinal disorders	117
HEPATOBILIARY/PANCREAS	5	Hepatobiliary disorders	16
INFECTION	236	Infections and infestations	76
MUSCULOSKELETAL/SOFT TISSUE	37	Musculoskeletal and connective tissue disorders	41
OCULAR/VISUAL	21	Eye disorders	25
PULMONARY/UPPER RESPIRATORY	33	Respiratory, thoracic and mediastinal disorders	59
RENAL/GENITOURINARY	62	Renal and urinary disorders	20
SURGERY/INTRA-OPERATIVE INJURY	141	Surgical and medical procedures	1
		Injury, poisoning and procedural complications	78
SEXUAL/REPRODUCTIVE FUNCTION	16	Reproductive system and breast disorders	51
		Pregnancy, puerperium and perinatal conditions	5
		Congenital, familial and genetic disorders	1
VASCULAR	21	Vascular disorders	17
SECONDARY MALIGNANCY	1	Neoplasms benign, malignant and unspecified	5
METABOLIC/LABORATORY	31	Metabolism and nutrition disorders	24
COAGULATION	6	Investigations	38
BLOOD/BONE MARROW	13	Blood and lymphatic system disorders	11
NEUROLOGY	47	Nervous system disorders	63
		Psychiatric disorders	20
—		Social circumstances	2
LYMPHATICS	10	—	
DEATH	4	—	
HEMORRHAGE/BLEEDING	51	—	
PAIN	54	—	
SYNDROMES	7	—	
Total	1,059	Total	790

Some of the most notable changes:

- The AEs in the former categories of Death, Hemorrhage/Bleeding, and Pain have been incorporated in the relevant disease SOCs.

- Activities of Daily Living (ADL) is now divided into two levels, which frequently determine whether an event is a grade 2 or grade 3:

  - Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

  - Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- The Death due to Progressive Disease AE no longer exists. Every effort should be made to classify deaths as grade 5s in appropriate AEs; when this is not possible, they may be classified as Death, NOS.

- "Disabling" is now used as a criterion for grade 3, vs. grade 4 in previous versions.

- SWOG is establishing policies for the use of some new AEs:

  - "Surgical and medical procedures" should be not be reported as SAEs or adverse events unless explicitly so directed in a protocol.

  - "Surgical and medical procedures," "falls," and "infusion site extravasation" should not be reported in an expedited manner as SAEs unless clearly associated with other reportable SAEs.

  - "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" should not be reported as SAEs unless possibly, probably, or definitely attributable to protocol treatment. (Per NCI policy, occurrences of AML, ALL and MDS in patients who are or have been on NCI protocols should be reported only on the NCI/CTEP Secondary AML/MDS Report Form.)

The following links are to tools that will aid in the transition to and use of this new method of reporting. They are all listed on the Serious Adverse Events page in the Members section of swog.org.

- CTEP CTCAE 4.0 web page   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

- PDF versions of 4.0:

  8½ x 11" size   CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

  5 x 7" size   CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

- On-line lookup tool   http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx
  (for 2.0, 3.0, and 4.0)

- Slide Shows:

  SWOG's Introduction to 4.0   https://swog.org/Members/download/AdverseEvents/CTCAE40.pps

- This handout   https://swog.org/Members/download/AdverseEvents/CTCAE40.pdf

- Ordering printed booklets   https://cissecure.nci.nih.gov/ncipubs/detail.aspx?prodid=P186
  (Projected availability: May 2010)