

Manual for the Completion of caBIG™ Case Report Form (CRF) Modules

Introduction

In 2006, members of the Cancer Biomedical Informatics Grid or caBIG™ in conjunction with the National Cancer Institute's Center for Biomedical Informatics and Information Technology (NCI CBIIT) initiated a Case Report Form (CRF) harmonization activity. CRFs submitted from the community were reviewed and inventoried. The Harmonization group then reviewed all questions on the CRF and partitioned them into three categories:

- Mandatory – must be included when this data is collected for reporting
- Conditional – there are business rules to indicate situations under which this element should be used on a CRF
- Optional – no requirement for inclusion of this element on the CRF; if the design and scientific questions posed in the study dictate the need to collect this type of data, this is the element to include on the CRF

A template form with modules that contain questions or variables representing data to be collected was developed. The companion eCRF instruction manual is a set of directions to guide data collection in each module template. Specific implementation instructions are not present; various groups may wish to implement the contents of a module in a variety of software applications.

The instructions include the field name, description or definition of each field, and any special formatting notes that apply to entries – such as the inclusion of full dates, use of values from a choice list only, etc.

Finally, each question (or data item) is noted as Mandatory (m), Conditional (c), or Optional (o).

Adverse Event Module Definition

The Adverse Event CRF module is used to document Adverse Events (AEs) experienced by the participant on cancer clinical trials. In order to capture all Adverse Event data in a similar way, this module will be used to capture baseline symptoms/conditions, AEs experienced during protocol therapy, and those identified during the follow-up period.

Although the AEs of primary interest are those attributable to the protocol intervention, all Adverse Events are documented and available for analysis, including those attributable to the disease and/or concomitant medications. As a result, the definitions currently appearing in the NCI Thesaurus and those developed by CDISC and other authorities are not always comprehensive enough.

Adverse Event Module Options

For the most part, Adverse Events observed during protocol treatment are documented following each cycle or course of treatment (depending on the sponsor and/or trial type). During the follow-up period, evaluation visit timeframes are usually established. As a result, a mechanism is provided to expedite entry of all AEs encountered during the assessment period.

Serious Adverse Events (SAEs), on the other hand, should be reported in expedited fashion to the appropriate protocol, sponsor, and regulatory staff. Therefore, a mechanism is also provided to facilitate entry of a single Adverse Event as it occurs by simply using the AE and SAE subsections formatted for a single AE. For SAEs, this final section will always be collected to identify why it is considered serious and to capture information needed to establish the reporting requirements.

Note that the term 'serious' is deceptive in that a reportable AE may not always be considered serious in terms of severity of the event itself. There are instances in which an Adverse Event requires expedited/special reporting since it is medically significant (for instance, one that is a lower grade but occurs frequently enough to be of concern). The 'rules' for what constitutes an SAE are dependent on the sponsor and the protocol itself.

Template Instructions

The AE CRF consists of 3 sub-modules:

1. Form Level information is collected when Adverse Events are recorded for a period of time (e.g. a cycle, course, or period since the last visit). This section captures data related to the period covered by the data in the section below. On this type of CRF, the section below would facilitate entry of multiple AEs more efficiently.
2. The primary AE module captures data on all Adverse Event data. Note that in addition to the 'untoward events', this section may capture information about Solicited Adverse Events – these are events that the protocol is specifically targeting and the study participant will be evaluated for each of these conditions. Grade 0 (not evident) is possible for this type of AE.
3. Serious Adverse Events (those that are actually termed 'medically important') require collection of a small amount of additional information. If an AE is deemed 'serious', the data in this section is collected to complete the submission for that event.

Field Descriptions and Instructions

Form Level Data Elements

Field Name/Status	Description/Instructions	Format
Start of AE Evaluation Period (c)	Date of the beginning (start) of the assessment period.	Date. Use would depend on how AEs are collected. If you do not collect AEs on a single form that covers a period of time, this entire section would not be needed. For baseline assessments, the start of the evaluation would not be used (only the end of the evaluation period which would be the day before protocol therapy began). Some sponsor use an implied start date since the assessment period would begin immediately following the previous assessment period.
End of AE Evaluation Period (c)	End of the assessment period. The end of this evaluation period should be 1 day prior to the start of the next evaluation period (e.g. contiguous assessment periods)	Date.
Course # (c)	Episode marking a period of activity related to protocol intervention. May be used during protocol therapy period to automatically set the evaluation start/end dates to the period of the course of treatment (e.g. user supplies course# and evaluation period derived).	Number
Cycle# (c)	A repeating period of activity involving treatment and rest. Several cycles can make up a course	Number
Were AEs identified during this period? (c)	Indicator to clarify whether any AEs were identified during the reporting period. This is confirmation that the remainder of the form was intentionally left blank.	Yes/No/Unknown Unknown should not be available during reporting of AEs during protocol intervention.
Comment (o)	Provide additional information related to this SAE	Free text A general comment that should not be specific to a single AE.

Adverse Event Data Elements

Field Name/Status	Description/Instructions	Format
AE Evaluation Date (symptom assessment) (c)	Date on which the AE was first identified to protocol staff; this starts the clock ticking for reporting purposes. For solicited AEs, this would be the only date provided since there is no 'onset' of symptoms.	Date
AE Onset Date (Start Date) (c)	Date on which the AE was first evident.	Alpha DVG date to enable entry of partial dates (for baseline symptoms) or UNK.
AE Onset Time (o)	Time of Day when AE was first evident. Used when Date of Onset is insufficient. For example, when an event occurs before or within a short time after first treatment date, a time may be required.	Time
Pre-existing? (o)	Did this AE (with the same grade) exist in the period immediately prior to the reporting period?	Yes/No Should be derivable if you capture AEs for specified periods; not needed if you track an AE until it resolves (including worsening) rather than for a defined assessment period.
AE Resolved Date (Stop Date) (c)	Date on which the AE resolved. Need to be clear whether the AE resolved so 'ONG' can be used OR a separate Ongoing flag set.	Alpha DVG date
AE Resolved Time (Stop Date) (o)	Time of day when AE was resolved	Time
AE Ongoing? (o)	Flag to indicate whether AE has resolved or not. This ensures that leaving 'Stop Date' blank was not done inadvertently. [Many in group feel that blank date means the same thing so this isn't needed]	Yes/No
AE Type Code (m) MedDRA Adverse Event Code (m)	Code used to identify the adverse event using a standard mechanism that facilitates analysis. CTEP's code list and associated Category/Term is currently a standard.	CTEP/MedDRA codes for Adverse Events
AE (Symptom) Description (verbatim) (c) but highly recommended	Verbatim AE Description used to 'reinforce' selected AE Type Code	Free Text Field
AE Other, Specify (m)	AE clarification required when an AE Type Code is not specific enough (e.g. corresponds to a general category – other, specify). May be handled via verbatim.	Free Text Field

AE Grade (m)	A coded value to identify the severity of the adverse event.	CTCAE Grades of 0 (for solicited AEs) through 5.
Attributable to Study Intervention (c)	<p>In the opinion of the treating physician, what is probability that this AE is related to the study intervention?</p> <p>This question is not asked for baseline assessments. Question should be asked (mandatory) for all studies that involve drug therapy.</p>	<p>Yes, No, Uncertain/Possible (3 choices)</p> <p>Similar to question 'Intervention/Research Related'. Group felt that 'attribution' is more commonly understood in oncology environment.</p> <p>Current categories are open to too much interpretation (e.g. difference between probable and possible is difficult to tease out). However, yes/no is not adequate.</p> <p>Also, difficult to determine which drug in a multi-drug regimen is responsible for AE.</p>
What is most likely cause of the AE? (c)	<p>In opinion of the treating physician, what is the most likely cause of the AE?</p> <p>Should be required for all serious AEs but not necessarily for non-serious.</p>	<p>List of other therapies (surgery, radiation, etc), disease, concomitant meds, other. Select MOST likely.</p>
Cause Other (c)	<p>If 'other' selected in data element above, must provide a description of the presumed cause.</p>	<p>Free text field</p>
Was patient hospitalized or hospitalization prolonged as result of this AE? (c)	<p>Conditional upon AE being a grade 3-5 for CTEP; DCP asks this for all AEs. Normally required only if AE is deemed 'serious'.</p> <p>Response needed to determine reporting requirements for certain sponsors.</p>	<p>Yes/No</p>
Serious (m)	<p>Is the AE considered a medically important event based on the criteria in the protocol and/or as determined by the PI?</p> <p>If a 'yes' response is entered, complete the SAE section for this AE.</p>	<p>Yes/No</p>

Serious Adverse Event Data Elements

Field Name/Status	Description/Instructions	Format
Seriousness Criterion (m)	Why is the AE deemed to be medically important (serious)?	List of values
Dose Limiting Toxicity? (c)	Usually used only for phase I trials. Does this AE constitute Dose Limiting toxicity?	Yes/No
Pt Status/Outcome (c)	What is patient's status as a result of this AE? Used by pharma. Suggest that this information be collected in Course Assessment since it is usually not specific to 1 AE. Much of this information is also available via the Date Resolved and Grade (5-died) data elements.	List of values
Event Pattern Code (o)	Is this a single event or continuous? This should be derivable from a review of AEs over time.	List of values
Event Reappeared After Reintroduction? (o)	Is this event a reoccurrence after reintroduction of protocol therapy?	Yes/No

NCI Adverse Event Module Template

Mandatory Questions

AE Type Code

CDE: 2002150 CTC Adverse Event Term Code (although may use other vocabularies in future)

MedDRA Adverse Event Code

CDE: 2538246 CTC Toxicity Type Code

AE Other, Specify

CDE: 3288 CTC Adverse Event Term Specify (would like CTC taken out of CDE name; not protocol specific list)

AE Grade

- 0 – No Adverse Event or Within Normal Limits
- 1 – Mild Adverse Event
- 2 – Moderate Adverse Event
- 3 – Severe Adverse Event
- 4 – Life-threatening or Disabling Adverse Event
- 5 – Death Related to Adverse Event

CDE: 2201188 CTC Adverse Event Reporting Grade

Serious?

CDE: 2199908 Serious Adverse Event Indicator (would like reference 'medically important' added)

Seriousness Criterion (mandatory for Serious AEs)

- 1- Resulted in death
- 2- Life threatening
- 3- Required hospitalization or prolongation of existing hospitalization
- 4- Resulted in persistent or significant disability/ incapacity
- 5- Resulted in a congenital anomaly/birth defect
- 6- In medical judgment of treating physician and/or investigator, jeopardizes participant or required intervention to prevent another serious outcome
- 7- Meets criteria per protocol but does not meet other criterion (above)
- 8- Other, specify

CDE: 2179679 Serious Adverse Event Description Reason Text

Conditional Questions**Start of AE Evaluation Period**

CDE: 2744943 Adverse Event Begin Assessment Date

End of AE Evaluation Period

CDE: 2006851 Adverse Event Final Assessment Date (although preferred question is better name)

Course#

CDE: 2732184 Protocol Course Number Count (suggest word 'count' be removed)

Cycle#

CDE: 2744948 Treatment Cycle Number

Were AEs identified during this period?

CDE: 2179971 Adverse Event Most Recent Assessment Ind-3

AE Evaluation Date (Symptom Assessment Date)

CDE: 2004170 Evaluation Date

AE Onset Date (Start Date)

CDE: 2744993 Adverse Event Onset Date

AE Resolved Date (Stop Date)

CDE: 2189843 Adverse Event Resolved Alpha DVG Date

AE Description (Verbatim)

CDE: 2188132 Adverse Event Verbatim Term Text

Attributable to Study Intervention?

Yes
No
Uncertain/Possible

CDE: 2746515 Adverse Event Attribution Study Indicator

What is MOST likely Cause of AE?

Chemotherapy
Combined Modality
Surgery
Radiation
Disease
Concomitant Meds
Other

CDE: 2179892 Adverse Event Cancer Treatment Related Type

Cause Other

CDE: 2188434 Adverse Event Other Therapy Descriptive Text (although not exclusive other therapy)

Was Participant Hospitalized or Hospitalization Prolonged as Result of this AE?

CDE: 2552398 Patient Toxicity Hospitalization Indicator (recommend removal of word 'toxicity')

Dose Limiting Toxicity?

CDE: 2004106 Dose Limiting Toxicity Ind

Participant Status/Outcome

FATAL
NOT RECOVERED/NOT RESOLVED
RECOVERED/RESOLVED
RECOVERED/RESOLVED WITH SEQUELAE
RECOVERING/RESOLVING
UNKNOWN

CDE: 2746518 Adverse Event Outcome Text Type

Optional Questions

AE Onset Time

CDE: 2585234 Adverse Event Onset Time

Pre-existing AE?

Yes
No

CDE: 2746280 Adverse Event Pre-Existing Indicator

AE Resolved Time

CDE: 2746301 Adverse Event Resolution Time

AE Ongoing?

Yes
No

CDE 2746311 Adverse Event Ongoing Event Indicator

Event Pattern Code

1- Single Episode
2- Intermittent
3- Continuous

CDE: 2008418 Adverse Event Condition Pattern

Event Reappeared After Reintroduction?

Yes
No
N/A

CDE: 2179615 Adverse Event Reappearance Indicator

Comment

CDE: 797 Research Comments Text