Serious Adverse Event (SAE) Reporting Reference Guide

This document provides standard reference language for the reporting of Serious Adverse Events (SAEs) in clinical trials.

Definition of a Serious Adverse Event (SAE)

An SAE is an adverse event that meets any of the following criteria:

• Results in death
Note: Death due to disease progression should not be reported as an SAE unless attributable by the Investigator to the study drug(s).

• Is life-threatening
Defined as an event in which the subject was at risk of death at the time of the event.
Note: This does not refer to an event that hypothetically might have caused death if it were more severe.

• Requires hospitalization >24 hours or prolongation of an existing hospitalization
Note: Hospitalizations for anticipated or protocol-specified procedures (e.g., chemotherapy, central line insertion, metastasis interventional therapy, primary tumor resection, or elective surgery) are not considered SAEs.

• Results in persistent or significant disability/incapacity

• Is a congenital anomaly or birth defect

• Is an important medical event
Defined as a medical event that may not be immediately life-threatening or require hospitalization but may, based on medical judgment, jeopardize the subject or require intervention to prevent other serious outcomes.
Examples: intensive ER/home treatment for allergic bronchospasm; blood dyscrasias or convulsions not requiring hospitalization; development of drug dependency or abuse.

Causality Assessment

Investigators must assess the causal relationship of each AE to the study drug(s). Key factors include: temporal relationship, known side effects, medical history, concomitant medications, disease course, and study procedures.

For patients on combination therapy, causality must be assessed separately for each drug.

Causality Guidance:

• Related: At least possibly related to study drug. Plausible temporal relationship, not explained by other causes, follows known pattern, abates on discontinuation/dose

reduction, may reappear on re-challenge.

• Not Related: Unlikely related to study drug. Evidence for other etiology or no plausible temporal relationship.

Adverse Events (AEs)

• Recorded from signed informed consent until 90 days after discontinuation of study drug(s) or until initiation of new anti-cancer therapy, whichever occurs first.
• All AEs are recorded, regardless of attribution.
• Documented in the medical record and on the study-specific eCRF.
• AEs related to study drug(s) must be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, or initiation of new anti-cancer treatment.

SAE Reporting to Agenus Inc.

All SAEs, regardless of attribution, must be reported to Agenus within 24 hours of awareness.

Reporting Methods:

• Email: Adverse.Events@Agenusbio.com
• Fax: +1-781-674-4261

Reports include:
• SAE Report Form (Agenus template)
• MedWatch FDA Form 3500A

Follow-up information, including updates or pregnancy outcomes, must be reported using the same timelines.

Reporting Timeframes

Report Type	Timeline
Pregnancy	Within 24 hours using Agenus Pregnancy Report Form
SAE (including pregnancies)	Within 24 hours using Agenus SAE Report Form and MedWatch 3500A

Pregnancy and In Utero Exposure

• Pregnancies related to study drug are AEs.
• All pregnancies with conception during study-defined exposure period must be recorded in the eCRF.
• Outcomes must be reported:
  - Abnormal outcomes/SAEs: within 24 hours

- Normal outcomes: within 45 days of delivery

• Patients must be discontinued from study drug immediately upon confirmed pregnancy.

Botensilimab and Balstilimab Dosing Errors

• Definition: Any dose deviating ≥10% from planned dose.

• Report all dosing errors, whether or not associated with an AE, using the SAE Report Form.

• Clinical judgment should guide management.

• Underdosing events must not be compensated at the next administration.

Events Not Considered SAEs

• Elective hospitalizations solely for study drug/procedures are not considered SAEs.

• Emergency visits or hospitalizations <24 hours are not automatically SAEs (unless medically justified as serious).

Events Not Considered AEs

• Baseline medical conditions that do not worsen during the study.

Disease Progression

• Symptoms associated with progressive disease must be recorded as AEs.

• If criteria for seriousness are met, they must be reported as SAEs.