ADVERSE EVENTS

If a patient experiences an unusual side effect, adverse event, or a serious adverse event complete the Adverse Event Form (AE).

An Adverse Event form should not be completed for expected side effects, such as the common side effects listed in the "Symptoms" section of the Treatment and Follow-Up Evaluation forms.

An adverse event is considered a serious adverse event if one or more of the following apply:

1. results in inpatient hospitalization or prolongs existing hospitalization
2. event is life-threatening
3. results in death
4. results in significant or permanent disability
5. requires medical intervention to prevent permanent damage
6. results in a congenital anomaly or birth defect

If the patient experiences a Serious Adverse Event:

1. Clinical center personnel complete the Adverse Event form and the MEDWATCH form.

2. The completed MEDWATCH form must be faxed to the Coordinating Center at the University of Pittsburgh within 24 hours of knowledge of the event.
   Fax: (412) 624-9489

3. The Coordinating Center will submit the MEDWATCH form to the Safety Officer (Dr. Geoffrey Block). The Coordinating Center will be responsible for distributing the report to the Data Safety Monitoring Board, clinical center Principal Investigators, and Dr. Patricia Robuck.

4. Dr. Patricia Robuck will be responsible for reporting to the FDA.

5. The Clinical Center and Coordinating Center Principal Investigators are responsible for notifying their local Institutional Review Board.

ADVERSE EVENT FORM (AE)

DATA SECTION	COMPLETION INSTRUCTIONS
GENERAL INFORMATION	The Adverse Event (AE) form is completed when the patient experiences a severe side effect, condition, or serious symptom. A form should not be completed for the presence of common side effects such as those captured in the "Symptoms" section of the Treatment Evaluation. At a minimum, the following criteria should be used as a guide for recording Adverse Events. 1. A symptom or event that requires a dose reduction or discontinuation of study medication. Exception: If a dose reduction is prescribed as a result of neutropenia, anemia, or thrombocytopenia, the event does not need to be recorded as an adverse event. 2. A newly diagnosed symptom or event that requires a written prescription for treatment. 3. A newly diagnosed symptom or event that results in a referral to another provider. 4. Any grade 3 or 4 event according to the WHO criteria. These guidelines are not all inclusive and the recording of an adverse event remains at the discretion of the investigator. A symptom or condition that is present but does not reach one of these levels may still be recorded as an adverse event. If the adverse event is determined to be a Serious Adverse event (SAE), complete a mandatory MEDWATCH form in addition to the Adverse Event Form and return the MEDWATCH form to the Coordinating Center at the University of Pittsburgh within 24 hours of knowledge of the event. Follow the detailed instructions in the Form Completion section of this manual for AEs that evolve into SAEs. Each page of the Adverse Event form is designed to capture up to 10 events per patient. Each new onset of an adverse event should be recorded on one line of the Adverse Event form. If a patient has more than 10 adverse events, move to the next page. Each adverse event should have a date of onset and outcome date, regardless of the duration of the event. Do not record the same event on more than one line if the event is continuing from one evaluation to the next. Leave the Outcome Date and Outcome Status columns blank until the event either resolves or is determined to be continuing but controlled. If the Outcome Status is determined to be Continuing/controlled and then the patient has an exacerbation of that same event type, record the new onset on a new line. Only new onsets should be recorded on a new line.
PATIENT ID	Record the patient's ID number.
PAGE	Record the page number. Each page of the Adverse Event form captures up to 10 adverse events. Begin with page 1 for each patient and continue to add pages as needed.

DATA SECTION	COMPLETION INSTRUCTIONS
	SPECIFIC INSTRUCTIONS: Date of onset: Record the date (month/day/year) that the patient adverse event started. If any part of the date is unknown, record "Unk" in that field and complete the remaining fields. Event type: Record the code that indicates the event type. The codes are listed at the bottom of the Adverse Event form. Also, provide specification for the event on the back of the AE form, e.g. in the event of Death, specify the cause of death. Serious adverse event: Circle "Y" (yes) or "N" (no) to indicate if the adverse event is a serious adverse event. If yes, complete a MEDWATCH form and submit that form to the Coordinating Center within 24 hours of knowledge of the event. Severity: (1) Record the code that indicates the initial severity of the episode. (2) Record the code that indicates the "most severe" severity of the episode. 1 = mild 2 = moderate 3 = severe 4 = life threatening Relationship to study drug: Record the code that indicates the relationship of the event to each of the study medications. 1 = unrelated 2 = unlikely 3 = possibly related 4 = probably related 5 = definitely related Drug dosing: Record the code that indicates the effect of the event on each study drug dose. 1 = none 2 = reduced 3 = interrupted 4 = discontinued If there is a prescribed change in study medication dose, complete a Dose Change (DC) form. Action taken: Record the code that indicates the action taken for the adverse event. 1 = none 2 = additional therapy 3 = hospitalization 4 = re-evaluation of laboratory results 5 = other If other, specify the action taken within the box.

DATA SECTION	COMPLETION INSTRUCTIONS
	Outcome date: Record the date (month/day/year) of the outcome of the adverse event. If the adverse event is continuing but not controlled this column should be left blank until the event is resolved or continuing but controlled. Some events may continue through the end of the treatment period or follow-up period before being resolved or determined to be continuing but controlled. Outcome status: For each adverse event, record the code that indicates the outcome status. If the adverse event is continuing but not controlled record as Continuing. When the event is either Resolved or Controlled, update both the Outcome Date and Outcome Status on the form and in the database. If the adverse event evolves into a SAE, close out the adverse event by recording complete information for the AE until the time that it was determined to be a SAE. Record 'evolved into SAE' as the Outcome Status, and record the date that the AE was determined to be an SAE as the Outcome Date. Complete a new line for the SAE. The date of onset is the date that the AE was determined to be a SAE. Record all other information on that line pertaining to the SAE. 1 = Resolved: Event is resolved 2 = Continuing: Event is ongoing 3 = Controlled: Event is present but is controlled. 4 = Evolved into SAE: A continuing event that developed into a Serious Adverse event. Events that are coded as Continuing will be reviewed periodically throughout the course of the study to determine whether they have Resolved or are Controlled.