Investigator-Initiated Research (IIR) With Pfizer Products

Safety Reporting Reference Manual

(All Therapeutic Areas Including Oncology)

Contact Numbers*

Telephone: _____

Fax: _____

**Refer to your contract or your Pfizer contact for SAE reporting numbers if needed.*

Safety Reporting Reference Manual for Investigator-Initiated Research (IIR) With Pfizer Products

Introduction

This *Reference Manual* presents key information that you need to know in order to properly report to Pfizer Serious Adverse Events (SAEs) during your clinical trial. It covers safety reporting for all Pfizer products.

For Oncology Products

Reporting rules differ slightly for Oncology products (and also for mature Oncology versus newer Oncology products) and these differences are highlighted in special highlighted text boxes like this.

Why Must I Report SAEs to Pfizer?

- Pfizer has an ethical, scientific, and legal responsibility to collect and analyze safety information on its products so that the Company can:
  - Fully understand their benefit-risk profile
  - Provide accurate safety information to regulators, prescribing physicians, patients, and consumers
- As an investigator conducting research involving Pfizer products, you play an important role in partnering with Pfizer to monitor safety

You may also receive additional modules as follows:

IF…	**YOU WILL ALSO RECEIVE…**
Your study involves a Pfizer medical device	*Medical Device Complaint Reporting Guide*
Your agreement with Pfizer specifies that you will use the Investigator-Initiated Research Serious Adverse Event (IIR SAE) Form	*IIR SAE Form Completion Guide*

Note: Reporting an SAE to Pfizer does not relieve you from your responsibilities to report it to your local regulators.

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Investigator Responsibilities

Your primary responsibilities in the safety reporting process are to identify serious adverse events (SAEs) experienced by participants in your clinical study, forward the information to your local regulatory authorities and—as per your agreement—to Pfizer (or its designated contractor), and provide follow-up reports as requested.

Your responsibilities include:

- Collecting accurate data on all adverse events (AEs) that occur in clinical study subjects receiving Pfizer products (or blinded therapy) within the time periods specified on the following page, and obtaining information adequate to:
  - Assess whether an event meets the criteria for an SAE
  - Determine the outcome of each SAE
  - Assess the causality of each SAE
- Completing the Investigator-Initiated Research Serious Adverse Event (IIR SAE) Form (or other agreed-upon form for SAE reporting), and submitting it to Pfizer or a designated contractor immediately for a death or life-threatening event, and within 24 hours for all other types of SAEs

Points to Note: Serious Adverse Event Reporting in Clinical Studies

- IIR SAE forms (or other agreed-upon form for SAE reporting) must be submitted for all SAEs in subjects receiving a Pfizer product or blinded therapy occurring in the specified reporting period as defined in your contract with Pfizer
  - Even those that are not study-drug-related (e.g., those associated with concomitant medications) must be reported
- The investigator's responsibility to report an SAE to local regulatory authorities remains unchanged, even though the event has been reported to Pfizer
- SAE reporting forms are NOT submitted for non-serious AEs observed in clinical studies

Special Reporting Rules for MATURE Oncology Products ONLY*

For studies with these products, SAEs are reported only if they fit into either of the following categories:

1. Death that is not due to cancer progression, occurring during the study up to 28 days post the last dose of study drug.
2. An SAE that is assessed by the investigator as both related to treatment with the Pfizer product and unexpected for that product.
   - An event should be considered "related" to the Pfizer product if a relationship between the event and product is at least a reasonable possibility, and "unexpectedness" should be based upon the single safety reference document defined in the protocol.

*For the purposes of the above requirement, mature, marketed products are considered to be products that have been marketed 5 years or more and are not being used in combination with other oncology products where the safety profile is not yet established or where a filing for the purposes of registration of the other oncology product may be considered.

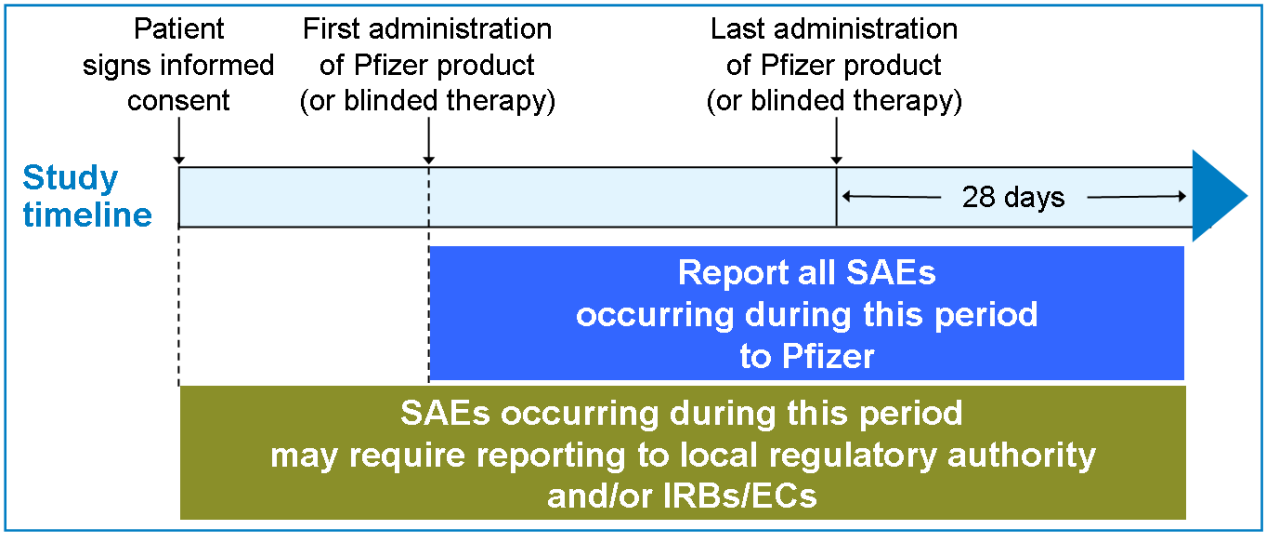
Clinical Study Time Period in Which SAEs Are Reportable to Pfizer

SAEs that occur during the following time period must be reported to Pfizer or its designated contractor:

- From the time that the subject receives the first dose of Pfizer product (or blinded therapy)…
- …through and including 28 calendar days after the last administration of the Pfizer product (or blinded therapy)
  - This time frame may be extended based on product characteristics (e.g., long half-life) or known safety profile, but it will never be less than 28 days under any circumstances

Note: The above statements refer specifically to reporting to Pfizer. Your local reporting responsibilities may begin when the subject signs informed consent for your study, as shown below.

Local Reporting Responsibilities Versus Reporting to Pfizer



Special Time Frame Rule for MATURE Oncology Products ONLY*

In addition, all **related** SAEs that the investigator becomes aware of after the reporting period should also be reported.

Required Reporting Time Frames

The time frame for reporting an SAE is:

- **Immediately**, if the SAE is fatal or life-threatening—regardless of the extent of available AE information

  but always

- **Within 24 hours** after the SAE occurs, or from the time when you (the study investigator) first become aware of the SAE:
  - Whether or not there is a suspected causal relationship to the Pfizer product or blinded therapy and regardless of the product labeling

Note: The above time frames also apply to additional new information (i.e., follow-up information) concerning previously submitted reports of an SAE.

Reporting Process

A report of a clinical study SAE must contain at least the following **four** elements:

1. An identifiable subject(s)*
There must be sufficient information that an SAE has been experienced by a specific individual. *Note: Patient names are NOT needed to meet this requirement.*
2. Suspect product
The report must name (or clearly refer to) a Pfizer drug, biologic, medical device, vaccine, nutritional product, over the counter (OTC) product, or blinded therapy. *Note: It is NOT necessary to break the study blind to report an SAE.*
3. SAE
The report must contain at least a description of an SAE (diagnosis or signs and symptoms).
4. Identifiable reporting source
The report must contain information that clearly identifies the reporter (e.g., you, as the study investigator), establishing that there was firsthand knowledge of the identifiable subject.

*For non-interventional studies, potential medication errors or near misses may be reportable even if there is NO identifiable subject as long as there is an identifiable reporter, a suspect product, and a medication error or potential medication error or near miss.

Note: Do not delay completing and submitting the report in order to obtain further information beyond these minimum required elements. Although attempts should be made to obtain as much information as possible and to provide this information to Pfizer for inclusion in the initial report of an SAE, do not wait to forward a report once you have the four minimum elements.

Investigator Causality Assessment

What Is Causality Assessment?

- Determination of whether or not there is a **reasonable possibility** that the Pfizer product or blinded therapy caused or contributed to an AE
- Recorded on the IIR SAE Form (or other agreed-upon form for SAE reporting)
  - This form will also include a description of the SAE in sufficient detail to allow for complete medical assessment of the case and independent determination of possible causality

For cases where the Pfizer product or blinded therapy is NOT determined to be causally related to the SAE, provide information in the Narrative on **other possible causes** of the SAE, including:

- Concomitant medications, including any protocol-specified background treatment
- Other illnesses
- Study procedures

Follow-up Information

Your safety reporting responsibilities include reporting follow-up information reasonably requested by Pfizer to assist in the complete assessment of the SAE. When new, updated, or corrected information about a previously reported SAE is obtained, a follow-up report should be submitted.

Follow-up information is documented on an IIR SAE Form (or other agreed-upon form for SAE reporting), recording only data that are new or revised from the previous report. The follow-up report is then forwarded to Pfizer or its designated contractor.

Examples of Follow-up

- Information that is **missing or incomplete** at the time of the initial SAE report
- Information **not previously available** (e.g., an illness outcome, findings from a laboratory test performed later, or autopsy findings)
- **Changes or clarifications** regarding information in a previously submitted report
- **Additional information requested** by Pfizer about a previously reported SAE

It is important that new information regarding an SAE be reported immediately.

- If a report is delayed, then the reason for the delay should be reported
- Examples of reasons for delay:
  - Information missed due to clerical issues at the site
  - Correction of previously transmitted information

In the case of a subject's death:

- Submit follow-up information as soon as possible
- Include a summary of autopsy findings, where available

Note: When providing follow-up information, use the same adverse event term that was specified in the initial SAE reporting form, unless the follow-up information includes correction or clarification of the term.

SAE Definition

What Is a Serious Adverse Event?

An SAE is any adverse event,* without regard to causality, that:

- Results in death
- Is life-threatening (immediate risk of death)
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Results in a congenital anomaly or birth defect

  AND/OR
- Is an important medical event

Note: For precise definitions of some of these terms, refer to the SAE Criteria table on the next page.

*An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject following administration of a Pfizer product (or blinded therapy) or use of a Pfizer medical device. There does NOT need to be a causal relationship between the event and the treatment with or usage of the product/device.

SAE Criteria

An SAE is any adverse event that…	Definition
…is life-threatening	Places the patient/subject/consumer at risk of death at the time of the event. *Note: This does NOT refer to an event that might, hypothetically, have caused death if it were more severe.*
…requires hospitalization	Any inpatient admission to a health care facility, even if for less than 24 hours. (See next section for examples.) Hospitalizations also include **transfer within the hospital** to a more acute care setting. In such cases, the subject is already in the hospital at the time that Pfizer product (or blinded therapy) is started, and then an AE occurs requiring more acute care, so the subject is transferred. Transfer might be from the psychiatric wing to a medical floor or from a medical floor to the intensive care unit (ICU). A planned medical or surgical procedure is not, in itself, an SAE.
…requires prolongation of hospitalization	Any extension of an inpatient hospitalization beyond the stay anticipated/ required (as determined by the investigator or treating physician) in relation to the original reason for the initial admission. For protocol-specified hospitalizations in clinical studies, any extension beyond the length of stay described in the protocol meets the definition.
…results in persistent or significant disability	A substantial disruption of a person's ability to conduct normal life functions.
…is an important medical event	Any other medical event that, in the medical judgment of the investigator, would be considered an SAE because it: • May jeopardize the subject *or* • May require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition Important medical events also include **suspected transmission via a Pfizer product of an infectious agent**, pathogenic or non-pathogenic, or **development of drug dependency or drug abuse** of any product (whether a Pfizer product or any non-Pfizer product). *Note: Refer to next page for additional examples of important medical events.*

Note: An AE may be described as severe, but this may not mean it is serious. For example, a headache that significantly interferes with the subject's usual function might be assessed as "severe" in the clinical study documentation, but would NOT require reporting to Pfizer unless it met one of the criteria for an SAE. Alternatively, a heart attack requiring admission to hospital may be assessed as mild, but would still be classified as serious because it meets the criteria for an SAE.

SAE Criteria Examples

Examples of hospitalizations (due to an AE) that are for less than 24 hours and meet the inpatient hospitalization definition for seriousness:

1. A study subject is admitted to the hospital as an inpatient for an AE; tests are performed, the results are returned, and the subject is discharged—all within a 24-hour period
2. A subject is admitted to the hospital as an inpatient because of an AE and leaves the hospital (within a 24-hour period) against medical advice

In each case, the intent was to hospitalize the individual for the AE; therefore, these would be considered inpatient hospitalizations.

Examples of transfers to more acute care that meet the SAE criterion of hospitalization:

1. A subject on a medical floor is started on a study drug. He experiences chest pains and is transferred to the coronary care unit (CCU)
2. A subject receiving study drug while an inpatient in a psychiatric unit develops a fever, is diagnosed with a contagious infection, and is transferred to an isolation room on the medical floor

Examples where prolongation of hospitalization is due to an AE and is therefore subject to reporting to Pfizer as an SAE:

1. A hospitalized study subject begins receiving a Pfizer product; hospitalization is prolonged for 1 week longer than anticipated due to the development of cholecystitis
2. A subject is receiving blinded therapy in a clinical study involving a Pfizer product and is admitted to the hospital for a protocol-specific procedure; during the admission, the subject develops a fever and remains hospitalized for 1 additional week

Examples of an important medical event include:

1. Allergic bronchospasm requiring intensive treatment in an emergency room or at home
2. Blood dyscrasias (i.e., hematologic problems or blood cell abnormalities) or convulsions that do not result in inpatient hospitalization
3. A subject taking a Pfizer investigational product (or blinded therapy) becomes addicted to a non-Pfizer prescription pain medication

Lack of Efficacy

For clinical study AE reporting purposes, lack of efficacy is defined as:

- Failure of expected pharmacological action or therapeutic benefit

For therapeutic areas **other than Oncology**, reportability to Pfizer (on an IIR SAE Form or other agreed-upon form for SAE reporting) depends on the approval status of the product and its indication as per the table below.

Approval Status/Type of Pfizer Product	Lack of Efficacy (LOE) Reporting
Pre-approval	LOE alone is **NOT** considered an AE, and thus is not reportable as an SAE.
Marketed (i.e., approved) product for an approved indication	LOE alone should be reported to Pfizer when one or more of the following conditions are met: • It is associated with a serious adverse event, OR • The product is a vaccine or contraceptive, OR • The product (such as an anti-infective) is used for the treatment of a life-threatening condition (excluding HIV and Oncology [see below]) —— A life-threatening infection where lack of efficacy seems to be due to the development of a newly resistant strain of bacterium/virus/fungus previously regarded as susceptible should be reported —— A life-threatening situation where the medicinal product was not in fact appropriate for the infectious agent should not be reported
Marketed products for non-approved indications	LOE alone is only reported to Pfizer if associated with an SAE.
Anti-retroviral products	LOE (i.e., disease progression) without other associated SAEs is to be reported to Pfizer, for medical review by its Safety group, within the protocol-stipulated period from the last dose of study treatment. In these studies, hospitalizations due to progression of disease (in addition to those associated with other medical AEs) are considered an SAE and reported to Pfizer within the protocol-stipulated period from the last dose of study treatment.

Lack of Efficacy (cont'd)

Reporting Rules for Oncology Products ONLY

Safety reporting procedures regarding lack of efficacy in Oncology studies differ from those in other therapeutic areas.

The following requirements apply for SAE reporting for Oncology clinical studies, regardless of other AE reporting procedures and criteria, or the approval status of the product and/or indication:

- For malignancy with a fatal outcome during the study or within the study reporting period, the disease progression IS reported, with death listed as the qualifying SAE criterion
  - Malignancy resulting in death is reported as an SAE if it occurs during the 28-day SAE reporting period after the last dose of the investigational product, irrespective of any intervening treatment
- Progression of the malignancy should NOT be reported as an SAE
- Hospitalization due to signs and symptoms of malignancy progression does NOT require reporting as an SAE

Example of a hospitalization in an Oncology study that does not require reporting as an SAE:

Shortly after completing cycle 1 of study treatment, a subject in a study of metastatic renal carcinoma is hospitalized for radiotherapy due to worsening bone pain. Two weeks later he is discharged on opioid medication. For Oncology studies, this type of hospitalization is NOT reported as an SAE. Signs of disease progression based on measurements of malignant lesions by radiographic or other methods should NOT be reported as SAEs.

Summary of Reporting Rules for Mature Oncology Products

Reporting Rules for MATURE Oncology Products ONLY*

For studies with these products, SAEs are reported only if they fit into one of the following categories:

1. An SAE that is assessed by the investigator as both related to treatment with the Pfizer product and unexpected for that product.
2. Death that is not due to cancer progression, occurring during the study up to 28 days after the last dose of study drug.
3. A related SAE that the investigator becomes aware of after the reporting period.

*For the purposes of the above requirement, mature, marketed products are considered to be products that have been marketed 5 years or more and are not being used in combination with other oncology products where the safety profile is not yet established or where a filing for the purposes of registration of the other oncology product may be considered.

Exposure During Lactation

An exposure during lactation occurs if an infant or child may have been exposed through breast milk to an investigational Pfizer medicinal product during breastfeeding by a female taking the Pfizer product.

Information regarding exposure during lactation is submitted to Pfizer (or its designated contractor) on an SAE Report Form **within 24 hours of awareness of the exposure**. Appropriate follow-up is required to determine the occurrence an outcome of any adverse event in the infant.

Exposure During Pregnancy

Exposure During Pregnancy reports relate to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at any time during pregnancy to a Pfizer product (or blinded therapy). Although Exposure During Pregnancy is not considered an SAE, it may result in an SAE. Even when there is no associated SAE, **Exposure During Pregnancy is always reportable**.

All Exposure During Pregnancy information is submitted to Pfizer (or its designated contractor) in the Narrative section of an IIR SAE form (or other agreed-upon SAE reporting form), irrespective of whether an AE has occurred, **within 24 hours of awareness of the pregnancy and/or exposure**.

The report should include the anticipated date of delivery. The subject is then followed until the end of the pregnancy and Pfizer is notified of the outcome as a follow-up to the initial Exposure During Pregnancy report, using a standard form.

An Exposure During Pregnancy Occurs Through Either:

Maternal exposure

- A female subject becomes, or is found to be, pregnant either while receiving or having been exposed to a medicinal product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the medicinal product
- A pregnant woman may have an environmental exposure involving direct contact with a Pfizer product (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products by inhalation or spillage)

or

Paternal exposure

- A male subject has been exposed, either due to treatment or environmental exposure, to a medicinal product prior to or around the time of conception of his child and/or is exposed during the partner's pregnancy

Exposure During Pregnancy (cont'd)

If known, provide information about the mother and the pregnancy within the Event Narrative or other appropriate field of the agreed-upon SAE reporting form, as outlined below:

All dates should be in the international date format.

Mother Information—Pregnancy	
Current pregnancy	• Provide the first day of the mother's last menstrual period (e.g., "12Jun2010"). Provide a partial date if the full date is unknown (e.g., "Jun2010"). • Provide an estimate (e.g., from ultrasound) of the date of conception. Enter a partial date if the full date is unknown. • Provide the estimated delivery date.
Gestation at time of initial exposure (if known)	• Provide an estimate of the duration of pregnancy (in months) at the time of initial exposure to the medication, if known. • Otherwise, indicate which trimester—first trimester, second trimester, or third trimester.
Exposure to Pfizer products (and any other drugs taken during pregnancy, including prescription and over the counter products)	• Provide the name of the product, indication, start and stop dates (reason for stopping [if applicable]), formulation, and dose/frequency.
Recreational drug use	• Did the mother smoke during this pregnancy? If yes, provide the number per day. • Did the mother drink alcohol during this pregnancy? If yes, how often? Provide the frequency. • Did the mother use illicit drugs during this pregnancy? If yes, how often? Provide the frequency.
Obstetrical history	• Note if there was no previous pregnancy. • Otherwise, provide the number of previous pregnancies, number of other children with additional details regarding the outcome of any previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy). • Add information about any previous maternal pregnancy complications (e.g., premature rupture of membranes). Include details specifically describing any previous fetal/neonatal abnormalities, if applicable, referring to both structural malformation and any non-structural or long-term functional effects. • Also supply any history of sub-fertility.

(cont'd)

Exposure During Pregnancy (cont'd)

Mother Information—Pregnancy (cont'd)	
Relevant history	• This information may include any maternal risk factors for adverse pregnancy outcomes, including environmental or occupational exposures and maternal disease(s) (e.g., hypertension, diabetes, infection). Describe the course of the pregnancy and any treatments. • Also include any family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify the degree, if known). • Also specify any treatments for infertility; provide results of serology tests (e.g., rubella, toxoplasmosis); and specify dates of, and results from, antenatal check-ups (e.g., fetal ultrasound, serum markers).
Delivery	• Indicate whether there were any problems before, during, or after delivery. — If yes, specify the problem (e.g., fetal distress, delivery complications, abnormal amniotic fluid, abnormal placenta). — Specify the mode of delivery, such as: – Natural birth (i.e., vaginal delivery without medication or anesthesia). – Cesarean section.

Neonatal Information	
Outcome of pregnancy	• Enter the date the pregnancy ended, (e.g., "02Apr2011"). Enter a partial date if the full date is unknown (e.g., "Apr2011"). • Describe only one outcome: — Full term live birth Full term = live birth at 37 or more weeks of gestation. — Preterm live birth Preterm = live birth at less than 37 weeks of gestation. — Stillbirth also known as fetal death; refers to delivery of a dead child. — Spontaneous Abortion/Miscarriage Refers to premature expulsion from the uterus of the products of conception, the embryo, or of a nonviable fetus. Included in this category is "missed abortion" when the products of conception are reabsorbed and not expelled. — Induced/elective abortion Refers to the pharmacologically or surgically induced expulsion from the uterus of the products of conception, the embryo, or of a fetus. — Unknown • Indicate gestational age (as determined by LMP and/or ultrasound) at birth in weeks (if known).

(cont'd)

Exposure During Pregnancy (cont'd)

Neonatal Information (cont'd)	
Outcome of infant	**Describe only one outcome**: • Normal Newborn. *Provide the Apgar Score(s) (if known) at 1 and 5 minutes.* • Congenital Malformation/Anomaly. *Specify details in the space provided.* • Other neonatal problem/abnormality. • Include dysmaturity, neonatal illness, hospitalization, and drug therapies. • Unknown.
Infant details	• Indicate the gender (sex) of the infant at birth (i.e., Male or Female). • Record the infant's weight at birth in grams, or if weight in grams is unknown, record the weight in pounds and ounces.
Follow-up of infant (if known)	Provide details regarding: • Any malformation/anomalies diagnosed. • Developmental assessment. • Infant illnesses, hospitalizations, drug therapies, breastfeeding.
Fetal information (if applicable, e.g., in the event of an elective termination, spontaneous abortion, late fetal death)	Provide details (if available and as applicable) regarding: • Reason for termination. • Gestational age at termination. • Results of physical examination (e.g., gender, external anomalies) and pathology.

Exposure During Pregnancy (cont'd)

Paternal Information	
Relevant history	• Provide the father's age, if known, in years. • Provide the father's date of birth, if known, (e.g., 01Jul1973). Enter a partial date if the full date is unknown (e.g., Jul1973 or 1973). • Provide the father's occupation, if known. • Include any risk factors including environmental or occupational exposures (e.g., HIV/AIDS, toxins). • Include details of any family history of congenital abnormality/genetic diseases or consanguinity (with details regarding family relationships or lineage) between the parents (specifying the degree of consanguinity).
Exposure to products—were any drugs (e.g., over the counter or medical prescription) taken by the father during the mother's pregnancy?	• Indicate "No" if none were taken. • Indicate "Yes" if applicable and specify the following details, as known: — Product. — Indication. — Start date. — Stop date. – Provide the reason for stopping, if known. — Formulation. — Dose/frequency.
Exposure to products—recreational drug use	• Did the father smoke during the mother's pregnancy? If yes, provide the number per day. • Did the father drink alcohol during the mother's pregnancy? If yes, how often? Provide the frequency. • Did the father use illicit drugs during the mother's pregnancy? If yes, how often? Provide the frequency.

SAE Reporting for Exposure During Pregnancy Cases

If the **outcome of the pregnancy meets seriousness criteria** for immediate classification as an SAE, follow the procedures for reporting SAEs.

Examples of pregnancy outcomes that are SAEs:

- **Spontaneous abortion** (includes miscarriage and missed abortion)
- Stillbirth
- **Congenital anomaly** (including in an aborted fetus, or in a case of stillbirth or neonatal death)
- Neonatal death

In the case of **neonatal death**:

- Any neonatal death that occurs within 1 month of birth should be reported, **without regard to causality**, as an SAE

In the case of **infant death**:

- Any infant death that is assessed as possibly related to the in utero exposure to the Pfizer product or blinded therapy should be reported as an SAE

Safety Line Listings

Information regarding unexpected clinical study SAEs that are causally related to a Pfizer product (or blinded therapy) is provided to IIR investigators biannually in the form of an IIR Safety Line Listing. These line listings should be placed with your labeling documents for your study files.

Note: Distribution of these Safety Line Listings by Pfizer does not replace the investigators' obligations for reporting safety information to their local regulatory authorities according to local regulations.