Tip #1: Terms to know

- **Adverse Event (AE):** any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- **Adverse Device Effect (ADE):** Adverse event related to the use of an investigational medical device.
  - This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
  - This includes any event that is a result of a use error or intentional misuse.
- **Serious:** An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - Serious injury
- **Serious injury:** an injury or illness that:
  - Is life-threatening,
  - Results in permanent impairment of a body function or permanent damage to a body structure, or
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
- **Life-threatening:** An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- **Permanent:** irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.
- **Unanticipated:** not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application)
- **Unanticipated Adverse Device Effect (UADE):** any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death:
  - was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or
  - any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects
- **Significant Risk Device (SR):** An investigational device that:
  - is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;
  - is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
  - otherwise presents a potential for serious risk to a subject.
- **Non-Significant Risk Device (NSR):** An investigational device that does not meet the definition of a Significant
### Risk Device.

**Tip #2: Your responsibilities as the Investigator**
- Document all adverse device effects in your patient study subject records
- Determine and document if the adverse device effect meets any of the definitions of **seriousness**
  - Determine and document *your assessment* about whether the adverse event may be **caused by** the investigational product
- Determine if and who needs to be informed of the event based on your determinations above
  - Sponsor
  - IRB
  - Others
- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event

**Tip #3: Your additional responsibilities as the Sponsor and IDE holder**
- Make final determination if the adverse event is **anticipated**
- Make final determination whether there is a **reasonable possibility that the device caused by, or associated with** the event.
- Make a final decision if the event is a **UADE**
- Sponsors must immediately conduct an evaluation of a UADE, and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

**Tip #4: If your IDE studies the effect of an already marketed device**
- All UADEs that occur in subjects enrolled in the clinical trial must be reported under your IDE. This applies to a device that is already marketed in the U.S. and if the device is not marketed in the U.S. but in a foreign country.

**Tip #5: What events to report to the FDA, the IRB and participating investigators, and how**
- As sponsor you must report to the FDA any event that meets **all three** of the definitions:
  - Adverse device effect
  - Serious
  - Unanticipated
- The report must be done in the form of an IDE safety report
- These UADE reporting requirements apply to both significant risk (SR) and non-significant risk (NSR) studies
Tip #6: How quickly to submit the IDE Safety Report to the FDA, reviewing IRBs and all participating investigators

INITIAL REPORT

- The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.
- Should the Sponsor determine that an unanticipated adverse device effect presents an unreasonable risk to research subjects, the Sponsor may terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after making this determination and not later than 15 working days after the Sponsor first receives notice.
- The day of initial receipt for cases that are interpretable as single cases and the day the sponsor determines that multiple cases qualify for expedited reporting are considered day zero.
- If FDA requests any additional data or information, the sponsor must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request.
- Sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review of safety information, including the frequency of review. FDA expects that events that are interpretable as single cases (i.e., uncommon and known to be strongly associated with device exposure) should be reported to FDA within 10 days from initial receipt. For events that require more than one occurrence to assess causality and events evaluated in the aggregate, the time clock starts when the sponsor determines that the events qualify for expedited reporting. This means that, for example, incomplete cases should be immediately followed up for additional information so that a determination can be made about whether the event is reportable as an IDE safety report.

FOLLOWUP INFORMATION

- If any information necessary to evaluate the suspected adverse reaction is missing or unknown, the sponsor should actively seek such information from the source of the report. Any relevant additional information that the sponsor obtains that pertains to a previously submitted IDE safety report must be submitted as a Followup IDE Safety Report without delay, as soon as the information is available, but should be submitted no later than 10 calendar days after the sponsor receives the information. The sponsor should maintain records of its efforts to obtain additional information.

Tip #7: IDE Safety Report Identification

- Each IDE Safety Report must prominently identify its contents. The label must be one of the following:
  - “IDE safety report” for 10-day reports
  - “Followup IDE safety report” for follow-up information
  - “The type of report should be checked in box G7 on the FDA Form 3500A. The report can also be identified in box B5 and/or on a cover letter submitted with the FDA Form 3500A.

Tip #8: IDE Safety Report Format

INDIVIDUAL CASES

- For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A. FDA will accept foreign Unanticipated Adverse Device Effect reports on a CIOMS I Form instead of FDA Form 3500A. These forms should be completed with all available information, including a brief narrative describing the Unanticipated Adverse Device Effect and any other relevant information. If applicable, the narrative must also include identification of similar reports and an analysis of the Unanticipated Adverse Device Effect.
AGGREGATE REPORTS

- An IDE safety report based on data in the aggregate must be in a narrative format. Sponsors should use judgment in deciding what to include in the narrative report. The report should include a description of the Unanticipated Adverse Device Effect, along with all relevant information, such as summary information about symptoms, concomitant medications, demographics, comorbid conditions, past history, pertinent laboratory test results, timing of events (onset and duration), and duration of treatment. Data from previously submitted individual case IDE safety reports should be included, if applicable. Finally, the narrative report should describe the characteristics and results of the analysis, including a description of the databases, how the conclusion was reached, who reviewed the analysis, any planned changes in monitoring or to study documents (e.g., informed consent, product description), and any planned further analyses.

- To evaluate the aggregated data in narrative format, FDA and participating investigators need the information on the individual cases that are summarized in the report. Therefore, at the same time that the narrative format IDE safety report is submitted, the individual cases that were analyzed should also be submitted (e.g., a completed FDA Form 3500A for each case). If some individual cases were previously submitted as IDE safety reports, they should be resubmitted and clearly identified as duplicates.

- The sponsor should determine an appropriate approach for reporting subsequent occurrences of the same event to FDA, all reviewing IRBs and all participating investigators, and the sponsor should include a description of this approach in the initial expedited narrative IDE safety report.

Tip #9: Where and How to Submit

- The report must be transmitted to the CDRH review division that has responsibility for review of the IDE.

- The sponsor should reference all IDEs to which the IDE safety report is being submitted in the subject line of the cover letter. If applicable, the sponsor should also identify (e.g., with use of an underline) the specific IDE under which the Unanticipated Adverse Device Effect occurred (e.g., "Unanticipated Adverse Device Effect occurred under IDE XXXX1, reference to IDEs XXXX2, XXXX3").

Tip #10: Where else do I need to report new adverse information?

In your next IDE Annual Progress Report to the FDA (only applicable if you hold an IDE)

- “Risk Analysis” section
  - Summary of any new adverse information (since the last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
  - Reprints of any articles published from data collected from this study
  - New risk analysis, if necessary, based on new information and on study progress

Tip #11: For more information, go to:

Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection

IDE Responsibilities.
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046702.htm


FAQs about IDE

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051480.htm#adverse

IDE Reports/ Suggested Format for IDE Progress Report

http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046717.htm#sugforforidepro

Form FDA3500A:

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

- If you have additional questions or would like assistance, please call the Clinical Research Support Center at (303) 724-1111 or email clinicalresearchsupportcenter@ucdenver.edu