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A New Standard for Medical Device Adverse Event Classification

By Nancy J. Stark

Adverse events are defined and managed differently in the device world than in the drug world. These differences are among the most difficult concepts for pharmaceutical people to understand.

In the pharmaceutical world, there is rarely a discussion of how to use the investigational product — how to swallow a pill is self-evident to most of us. When you think of a device, imagine using a new cell phone or a new kitchen stove or a new car. What happens if you push the wrong button? What happens if you drop it on the floor? Can you break the baking dish if you turn the oven up too high? Can you break your finger if someone shuts the door on your hand? Medical devices are mechanical, electrical and software-driven things. Think about what goes wrong with such things in your daily life and you'll have a better idea of what can go wrong with medical devices.

U.S. regulations (21 CFR Part 812 – Investigational Device Exemptions) are now 30 years old and not the best place to start in order to understand adverse events for medical devices. Furthermore, the device world is actively pursuing global harmonization, so looking at the requirements for FDA alone gives only a limited perspective on this topic.

Let's look at the new International Standards Organization (ISO) draft international standard ISO/DIS 14155 – Clinical Investigation of Medical Devices in Human Subjects – Good Clinical Practices (2009) and see how adverse events are classified in this document. When the new standard is officially published in 2010, it is expected to become the standard of practice around the world for medical device clinical research.

A New Approach to Adverse Event Classification

There have always been problems with adverse event classification in medical device clinical trials. Prior to the new draft standard, there was no mechanism for capturing complaints about devices that malfunctioned but did not result in subject injury. There was no mechanism for capturing investigator-use errors. There was no mechanism for capturing injuries to people who were not subjects.

At the most basic level, this article discusses two types of events: those that qualify according to the new draft standard to be handled in the study sponsor's adverse event system and those that do not. Events that *do not* qualify are handled by the sponsor as customer service issues according to corporate policies. Those that *do* qualify are subject to reporting requirements under the new draft standard, government regulations, and institutional review board (IRB) and ethics committee requirements. Specific reporting requirements for sponsors and research sites vary by country and will not be discussed in this article.

Decision Tree

It will help the discussion if you follow along on the decision tree in Figure 1. The tree is an adaptation of Annex F of the 2009 ISO/DIS draft standard. It begins with the observation that an untoward medical occurrence in either a subject (where we consider investigational devices, device-related procedures or comparators[1]) or other person (where we consider only the investigational device) has taken place, and progresses to classifying the complaint

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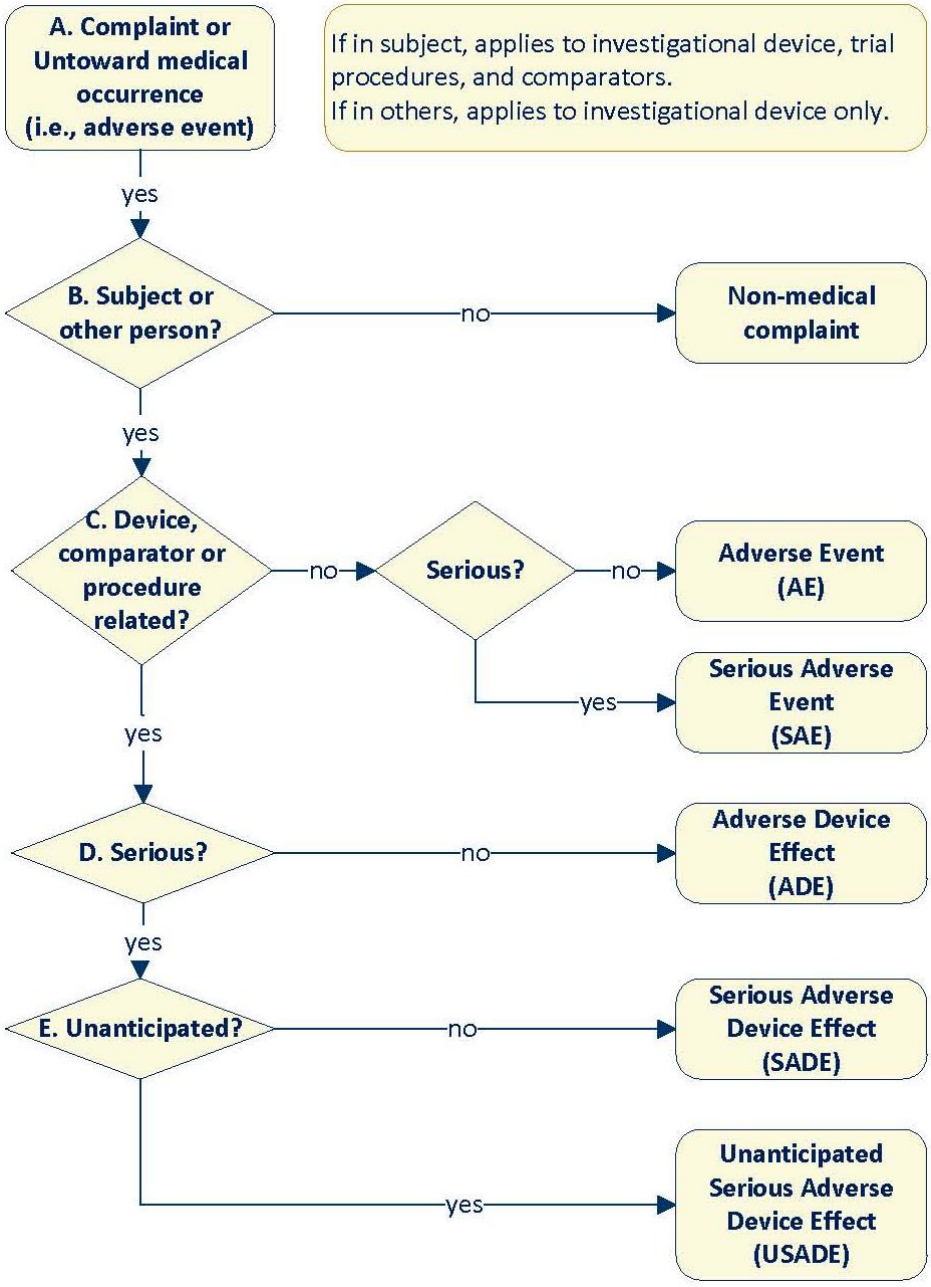
or untoward medical occurrence as either a non-medical complaint, adverse event (AE), serious adverse event (SAE), adverse device effect (ADE), serious adverse device effect (SADE), or unanticipated serious adverse device effect (USADE).

Figure 1. Decision Tree for Classification of Adverse Events



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Complaints (Box A)

Complaints are written, electronic or oral communications that allege deficiencies about an investigational device's identity, quality, durability, reliability, safety or performance. [2] If an investigational device complaint might have led to an untoward medical occurrence if: (a) suitable action had not been taken, (b) intervention had not been made, or (c) circumstances had been less fortunate, then it is handled under the sponsor's adverse event system.

However, if the complaint is not related to the investigational device, say it is about a different commercial device used coincidentally in the study (the scalpel is dull, the bed is hard), it is handled as a customer service issue.

Untoward Medical Occurrences (Box A)

The decision tree in the draft standard starts with the phrase "adverse event," but I find it confusing because the phrase is used again later in the standard to mean other things. To avoid confusion, I will borrow the opening phrase from the definition of "adverse event" — "untoward medical occurrence" — for Box A.

According to the draft standard, an untoward medical occurrence is an unintended disease or injury or untoward clinical sign in a subject, caregiver or other person caused by or related to the investigational device, device-related procedure, or comparator. If the untoward medical occurrence does not involve a subject, only occurrences related to the investigational device are included in the definition and handled by the sponsor's adverse event system. As shown in Table 1, the draft standard requires that the sponsor's adverse event system handle anything bad that (a) happens to the subject or (b) involves an investigational device.

Table 1. Complaints and Untoward Medical Occurrences

	Subject	Caregiver	Bystander	No Injury (Non-medical complaint)
Investigational Devices	✓	✓	✓	✓
Device -related Procedures	✓			
Comparator Devices	✓			

Investigational Devices

Untoward medical occurrences that are related to the investigational device and involve any person — a subject, caregiver[3] (e.g., investigator, study nurse, primary physician, parent or spouse), or bystander (janitor, company technician, or any other person, regardless of their relationship) — must be handled by the sponsor's adverse event system.

Device-Related Procedure

Untoward medical occurrences related to a device-related procedure and involving a subject must be captured by the sponsor's adverse event handling system. There is often a medical procedure involved in applying, implanting or using a device. The procedure itself — the act

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of casting a broken bone or inserting a stent through the femoral artery — may be the source of an untoward medical occurrence independent of the device.

The procedure for implanting, deploying, operating, applying or otherwise using an investigational device is as much investigational as the device itself. It may be that no one knows how to best use the investigational device, especially if it is a new technology. And, it is an accepted fact that investigators do not like to disclose device-related procedure occurrences because they feel it reflects badly on their competence. Only by requiring sponsors to capture the adverse event information can it be determined if cautions, precautions or warnings should be included in the device's labeling.

Comparator Devices

Untoward medical occurrences that are comparator-related and occur in subjects must be captured in the sponsor's adverse event handling system. In pharmaceutical trials, treatments are blinded, so handling adverse events related to the test article differently than those related to the control is not an option. Device trials are seldom blinded, so it is usually apparent whether the subject has received an investigational device or a comparator. Some have argued that capturing untoward medical occurrences from commercial comparator devices is unnecessary since they are already approved for sale. But that argument begs the question of why the trial is being done. Presumably, if there is a comparator device, the purpose of the trial is to compare the investigational device to it. It is necessary to capture untoward medical occurrences in comparator devices in order to make a safety comparison.

Non-Medical Complaints (Box B)

Not all complaints about investigational devices have to do with untoward medical occurrences, yet unless these complaints are captured there is no accurate way to assess device performance. If a complaint does not involve a subject or other person, it is obviously not medical and is called a "non-medical complaint." According to the draft standard, nothing more must be done in the sponsor's adverse event system, although the sponsor should use the information appropriately.

Table 2. Scenarios Leading to Non-Medical Complaints

Device mislabeled, instructions-for-use unclear, wrong lot number
Device malfunction
Performance failure
Investigator-use error

Let's consider some scenarios that might lead to non-medical complaints. For example, a device may be mislabeled, the instructions-for-use may be unclear, or it may bear the wrong lot number. Labeling errors that, perhaps by luck, do not result in an untoward medical occurrence in a person are non-medical complaints.

The device may malfunction during use. Malfunctioning may be as minor as a medical adhesive giving way too soon or as major as the lead of a pacemaker breaking. Neither event necessarily causes an untoward medical occurrence in a person, yet either event could be serious if the circumstances were right. The medical adhesive may be holding a life-supporting appliance in place. The broken pacemaker lead could prevent a critical electrical signal from reaching the heart. Device malfunctions that, even if by luck, do not result in a medical occurrence in a person are non-medical complaints.

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In a twist on the same concept, the device might simply fail to perform because of a design error. Nothing breaks, cracks or falls apart; the adhesive simply does not stick to skin or the pacemaker lead is too short. Devices that fail to perform as intended, yet do not result in an untoward medical occurrence in a person, are non-medical complaints.

In the final example, the device performs exactly as it is intended to perform, but the investigator makes an error in use. Suppose a reusable device is re-sterilized between uses but the re-sterilization process, itself, may cause the device to crack. The investigator is instructed to examine the device before each use to assure its physical integrity but fails to do so. The device is used on several occasions before damage is discovered. By luck, no one is injured. The event is a non-medical complaint if the investigator complains that the device isn't sufficiently durable.

Adverse Events (Box C)

Let's say the untoward medical occurrence did involve a subject or other person (Box B). The question then is whether the untoward medical occurrence (a) was related to the investigational device, device-related procedures or comparator, or (b) not. If not, and the occurrence is not serious, it is classified as an adverse event (AE).

So, adverse events are non-device-related, non-serious medical occurrences. Notice that the word "event" is used for untoward medical occurrences *not* related to the investigational device, procedure or comparator. We shall see later that the word "effect" is used for occurrences related to or caused by the investigational device, procedure or comparator.

Serious Adverse Events (Box C)

Let's say the untoward medical occurrence was not related to the investigational device or procedure or comparator, but resulted in serious injury to a subject or other person; then the occurrence is classified as a serious adverse event (SAE). Table 3 presents examples.

Table 3. Examples of Serious Adverse Events in a Trial Investigating Intraocular Lenses

Kidney ruptured in a bar fight
Passenger in a car accident
H1N1 flu
Salmonella food poisoning
A drug reaction

"Serious"

Serious adverse events are untoward medical occurrences in a subject or other person that are *not* related to the investigational device, comparator, or trial procedures, but that meet the criteria of "serious."

The definition of "serious" remains unchanged from the 2003 ISO standard and is very similar to the ICH good clinical practice definition. A serious adverse event is one that:

a) Led to a death,
b) Led to a serious deterioration in the health of the subject that:
    1) Resulted in a life-threatening illness or injury, or
    2) Resulted in a permanent impairment of a body structure or a body function, or
    3) Required in-patient hospitalization or prolongation of existing hospitalization, or
    4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

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A planned hospitalization for a pre-existing condition or a condition required by the protocol, without serious deterioration in health, is not considered serious.[4]

Part 812 is More Lenient

U.S. regulations for medical device trials — 21 CFR Part 812 – Investigational Device Exemptions — do not automatically require reporting of adverse events and serious adverse events. This comes about partly because the regulations are 30 years old and partly in recognition that about half the trials conducted in the U.S. are on non-significant-risk devices, such as toothbrushes, endoscopes, intravascular catheters, mammography devices, and ureteral stents.[5] The FDA explicitly informs the sponsor if it wants to see adverse events and serious adverse events reported for significant risk studies.[6]

Adverse Device Effects (Box D)

Let's consider an untoward medical occurrence that happened in a subject or other person and is related to the investigational device or device procedure (but not the comparator). If the occurrence does not meet the definition of serious, it is classified as an adverse device effect (ADE). Adverse device effects are a subset of adverse events.

Now, for the first time, we use the word "effect" in relation to a medical device adverse event, just as the word "reaction" is used in relation to a pharmaceutical adverse event. The phrase "device effect" is used with medical devices to convey the concept of "cause and effect."

Serious Adverse Device Effect (Box E)

An untoward medical occurrence that happens in a subject or other person, is related to the investigational device, comparator, or procedure, and is serious, but is *not unanticipated* is a serious adverse device effect (SADE). Untoward medical occurrences that are not unanticipated, i.e. are unsurprising, are identified in the investigator's brochure or protocol and informed consent form. The phrase "not unanticipated" is used instead of "anticipated" because "anticipated" suggests that the untoward medical occurrence *will* occur, while "not unanticipated" suggests it *might* occur.

One possible method of listing anticipated adverse device effects is to build a table like Table 4, in which the nature, severity, frequency of occurrence, and mitigation are presented. Later, this table can be used to establish whether or not a device effect was not unanticipated.

Table 4. Example List of Potential Adverse Device Effects

Nature of Effect	Severity	Frequency	Mitigation
Adhesive may dislodge	Mild	Common	Frequent inspection. Replace or reinforce tape
Positive airway pressure device stops functioning during sleep	Usually mild but possible severe if subject stops breathing	Rare	Run function tests nightly before going to sleep

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Unanticipated Serious Adverse Device Effect (Box E)

An untoward medical occurrence that happens in a subject or other person; is related to the investigational device, device procedure, or comparator; is serious; and was unanticipated is classified as an unanticipated serious adverse device effect (USADE).

U.S. and Japanese, but not European, medical device regulations include the USADE concept. Thus, if you are conducting studies with European investigators, extra training on this new concept is needed.

Summary

The new ISO/DIS 14155 draft standard brings welcome clarification and international harmonization to the classification of adverse events in medical device trials. The standard focuses attention on events most pertinent to human subjects protection. It will also streamline the activities of research sponsors, sites, IRBs, ethics committees, and regulators. As shown in Table 5, the classifications are logical and clear, although gray areas can always appear in practice.

Table 5. Medical Device Adverse Event Classification

	Involves Person	Involves Device, Procedure or Comparator	Serious	Unanticipated
Non-medical complaint	No	Device	n/a	n/a
Adverse Event (AE)	Yes	None of above	No	n/a
Serious Adverse Event (SAE)	Yes	None of above	Yes	n/a
Adverse Device Effect (ADE)	Yes	Any of above	No	n/a
Serious Adverse Device Effect (SADE)	Yes	Any of above	Yes	No
Unanticipated Serious Adverse Device Effect (SADE)	Yes	Any of above	Yes	Yes

References and Notes

1. Device trials that use a control almost always use an active control called a comparator. In most cases, a placebo or "no treatment" arm is unethical.
2. ISO/DIS 14155.2 (2009) Section 3.11, definition of a complaint.

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3. The draft standard uses the term "users," rather than "caregivers."
4. ISO/DIS 14155.2 (2009) Section 3.37
5. FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors; Significant Risk and Nonsignificant Risk Medical Device Studies
6. 21 CFR Part 812.3(m) defines a significant risk device as "an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject; (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health, safety or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject." A nonsignificant risk device is an investigational device that is not significant risk.

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