Harms and severities – Applying IMDRF and CTCAE

Background

Manufacturers sometimes struggle to determine adequate medical terms and to assign reasonable severity ratings as required by ISO 14971. In the past there was very limited guidance available discussing this task. In the meanwhile there were some helpful documents published making the challenge a bit easier and much more transparent.

In this short article, I want to share one simple way of making complex things a bit simpler. This may bring together the engineering point of view with the clinical and medical expertise. I want to remind you of

- IMDRF guidance on terminologies for adverse events and
- CTCAE Common Terminology Criteria for Adverse Events.

Applying IMDRF terminologies for adverse event reporting

The IMDRF published the guidance on terminologies for Adverse Event Reporting, which was now introduced into European vigilance reporting as well (http://imdrf.org/documents/documents.asp). The guidance aims to promote the use of defined terms as well as associated codes to describe problems encountered with medical devices. The guidance introduces different levels of terms. Annex E to the guidance provides the terminologies for clinical signs, symptoms and conditions.

Let's look into an example:

- IMDRF Level 1 term: Heart
  There are 24 supplemental terms listed. Let's look into two of them:
  - IMDRF Level 2 term: Cardiac Arrest (Code E0602)
    - IMDRF Definition: The sudden cessation of productive cardiac activity in an individual who becomes unresponsive, without normal breathing and no signs of circulation.
  - IMDRF Level 2 term: Ischemic Heart Disease, Angina (Code E061201)
    - IMDRF Definition: Chest pain resulting from inadequate oxygen delivery for the needs of the myocardium.

It can be seen, that the IMDRF Guidance will enable the determination of proper and precise terms. It will be possible to select relevant terms based on the definitions provided.

The terminology provided is actually based on MedDRA codes (like 10002383: Angina pectoris). MedDRA is an initiative by the ICH (https://www.meddra.org/) and IMDRF refers to MedDRA ("These terms are closely aligned to a subset of MedDRA terms, through close collaboration between IMDRF and MedDRA").

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Adding CTCAE severities

Subsets of MedDRA terms are used as basis for several other AE terminologies. One of those is the NCI's Common Terminology Criteria for Adverse Events (CTCAE) https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). A closer look into the CTCAE is quite helpful: The Common Terminology Criteria for Adverse Events (CTCAE), currently in version 5.0, provides terminologies for Adverse Event (AE) reporting.

Much more important, CTCAE includes a severity scale and a rating for each term. The rating proposed is made of 5 levels:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death.

Medical device practitioners will not be surprised to discover the 5-level-rating for severity as this is commonly used in medical device industries. Having this in mind, we will revisit our first example taken from IMDRF above:

- Cardiac Arrest (IMDRF Code E0602), defined as "The sudden cessation of productive cardiac activity in an individual who becomes unresponsive, without normal breathing and no signs of circulation."

The CTCAE document includes the term cardiac arrest as well and provides a definition and severity rating

- "A disorder characterized by cessation of the pumping function of the heart."
- The severity ratings are given from
    - Grade 4: Life-threatening consequences; urgent intervention indicated
    - Grade 5: Death

Surprised? Applying IMDRF and CTCAE, you will get well accepted terms for harm and the applicable severity ratings for FREE. For sure, each manufacturer will have to validate such terms and ratings for his specific devices and intended uses based on his own clinical and medical expertise. However, it is a great source of information going forward.

Will it also work for the second example above?

- Ischemic Heart Disease, Angina (IMDRF Code E061201), defined as “Chest pain resulting from inadequate oxygen delivery for the needs of the myocardium.”

  The CTCAE document includes the term chest pain as well and provides a definition and severity rating

  - “A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris.”
  - The severity ratings are given from
    - Grade 1: Mild pain
    - Grade 2: Moderate pain; pain on exertion; limiting instrumental activities of daily living; hemodynamically stable
    - Grade 3: Pain at rest; limiting self-care activities of daily living; cardiac catheterization; new onset cardiac chest pain; unstable angina

Again, it can be seen, that both documents, IMDRF guidance as well as CTCAE, fit together quite well. There will be some cases, were it may not work as good as above, but it is definitely worth trying it.

My conclusion:

If you are working in safety risk management for medical devices, you should consider, if the discussions above could help to establish a solid base for you risk analyses as per ISO 14971. It may be a great idea to validate your existing harms and severity ratings based on IMDRF and CTCAE.