Management of Risks and Benefits for Medical Devices

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Medical device safety is of paramount importance. Application of the international standard ISO 14971 is mandatory for obtaining approval for commercialization of medical devices. One of the requirements of ISO 14971 is demonstration that the residual risk of the medical device is outweighed by the benefits that it offers to the patients. This poses a difficult challenge for the medical device manufacturers, as risk and benefit are not easily comparable. This comparison must be done on each hazard and also on the overall system. Some of the challenges that device manufacturers face are: How do you determine the overall residual risk of the system? And, if you do determine the overall residual risk, how do you know if it is acceptable? How do you compare the residual risk against the benefit of the device? For example, if the benefit is improved quality of life, but at a 0.1 percent increased risk of death, which is greater — the benefit or the risk? This paper offers techniques and methodologies to provide objective evidence that the device design has met the risk benefit requirements of ISO 14971.

Introduction

While medical devices provide invaluable health benefits, they can also pose risks to human life and safety. It is understood that absolute safety cannot be guaranteed. Therefore, any benefits of a device need to be weighed against the risks of that device. Yet comparison of risks and benefits is challenging. For example, if the benefit of a medical device is an improved quality of life for the patient, but at a 0.1 percent increased risk of death, which is greater — the benefit or the risk?

This paper offers some practical techniques on how to systematically compare and evaluate the risks and benefits of medical devices.

History

The medical device industry is relatively new to system safety as a formal discipline. The aerospace industry began its interest in the 1940s. It wasn't until the 1960s, however, that safety requirements began appearing in aerospace systems. MIL-S-38130 — "Military Specification – General Requirements for Safety Engineering of Systems and Associated Subsystems and Equipment" — was published in 1963, followed by MIL-STD-882 in 1969. In contrast, it was not until the 1990s when the medical device industry began to pay attention to safety in a formal way. The first safety standard for medical devices, ISO 14971 — "Medical Devices — Application of Risk Management to Medical Devices" — was originally developed in 1998 with the participation of delegates from 112 countries. ISO 14971 was first released in 2000.

At about the same time that ISO 14971 was being developed, IEC 60601-1, Third Edition — "Medical Electrical Equipment – Part 1: General Requirements for Basic Safety and Essential Performance," was designed to include a risk management section. IEC and ISO organizations joined forces in forming JWG1 IEC/SC 62A to produce and release ISO 14971. The ISO designation was selected for 14971 because it has a larger scope than medical electrical equipment, which is the scope of IEC 60601-1.

Perception of Risk

As medical devices can directly impact the health and lives of patients, they carry a heavier perceived load on risks. Just as people are more afraid of dying in an airplane crash than in a car crash, even though statistically it is safer to fly than drive, so, too, medical devices are perceived as particularly risky. This has resulted in sometimes overly conservative engineering of medical devices, at increased cost and complexity. Using systematic and objective methodologies, such as those suggested in this paper, it is possible to produce medical devices that are effective and safe, without over-engineering.

Hazard Theory

In order to be harmed, there must be exposure to a hazard. As depicted in Figure 1, a sequence of events results in a hazard. A hazard is a potential source of harm. But there is no harm until there is exposure in a hazardous situation. Once exposure to a hazard occurs, harm can occur. However, not every exposure results in the same

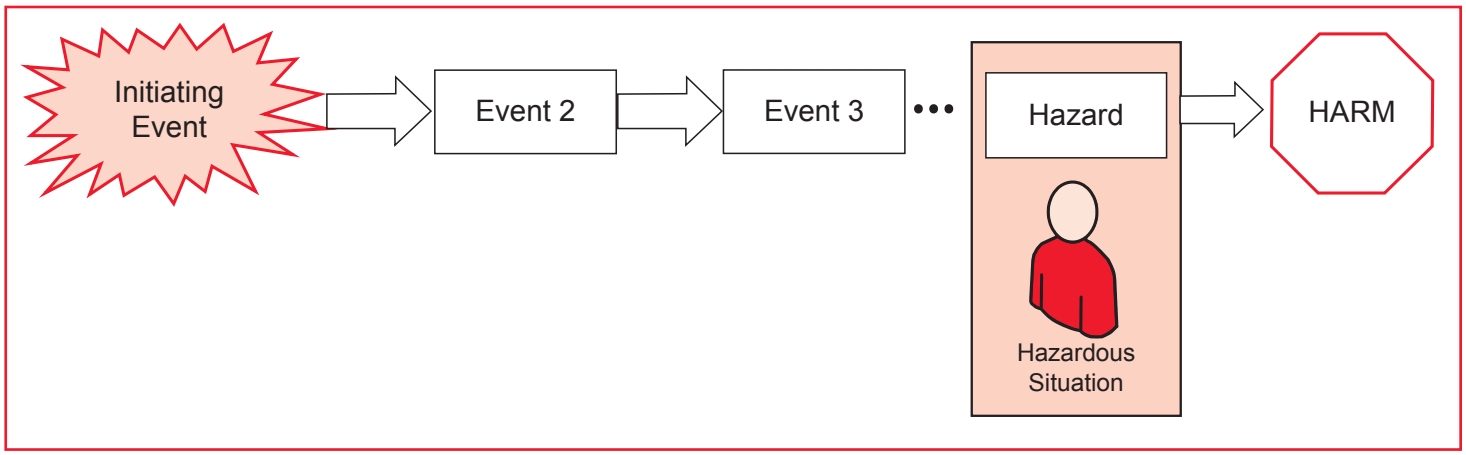

Figure 1 — Hazard Theory.

severity of harm. For example, exposure to the influenza virus can result in a range of harms from a minor fever to a catastrophic outcome: death.

Risk Calculation

Risk is the probability of experiencing harm. That is, the probability of exposure to a hazard *and* being harmed at a particular severity. Using the influenza example, let's say the probability of death from the influenza virus is 0.01 percent. The probability of catching the flu is about 12 percent. Therefore, the risk of death from influenza is the product of these two probabilities, or 1.2×10^{-5}.

Residual Risk Calculation Per Hazard

Residual risk is the risk that remains *after* all the mitigations to control the risk have been implemented. Typically, mitigations serve to reduce the probability of exposure to hazards, which we'll call P1. The probability of experiencing harm is P2. In the earlier influenza example, probability of exposure, P1, was 12 percent. Probability of death from exposure to the influenza virus, P2, was 0.01 percent. Let's assume a person took all feasible precautionary measures, e.g., taking a flu vaccine, avoiding sick people, washing hands, etc. Now, let's say the probability of exposure to the virus went down to 5 percent. The residual risk of death from exposure to the influenza virus becomes 5×10^{-6}.

Residual Risk Calculation (Overall)

Overall residual risk for a medical device refers to the risks from the device given the totality of all the hazards that the device presents. For example, let's say we are analyzing an infusion pump used to pump potassium chloride into a patient. For our purposes here, let's assume that the pump presents only three hazards: (bacterial) contamination, overdosing and underdosing. A patient could experience harm from any or all of these hazards. In our example, let's say only three harms are possible from these hazards: infection, hyperkalemia and hypokalemia. For this example, we'll focus on the catastrophic class of harm — death. Table 1 shows the first step in this computation. First, the risk of each harm (R) is computed. P1 is the probability of exposure to the hazard, and P2 is the probability of catastrophic harm from the exposure to the hazard. In Table 1, the risks are symbolically identified as R1, R2 and R3.

Next, the overall residual risk of catastrophic harm is computed. The Venn diagram in Figure 2 illustrates the contributions to risk of death from all the hazards that are presented by the infusion pump in this example. Note that since overdosing and underdosing are mutually exclusive, so, too, are hyperkalemia and hypokalemia.

The residual risk of death due to the infusion pump in this example is computed using Boolean algebra.

Overall residual = 1- (1 - R1) • (1 - (R2 + R3))
= 1 - (1 - 1.0E-5) • (1 - (4.5E-6 + 5.0E-8)) = 1.5E-5

Now that the overall residual risk has been determined, the risk should be evaluated for acceptability. Risk is acceptable if it is outweighed by potential benefit.

Establishing the Risk Acceptability Basis

One of the ways in which risks due to certain hazards can

Table 1 — Sample Risk Calculation Table - Per Hazard.

Hazard	P1	Harm	P2 Catastrophic	R Catastrophic
Contamination	1.0E-3	Infection	1.0E-2	1.0E-5 (R1)
Overdose	5.0E-5	Hyperkalemia	9.0E-2	4.5E-6 (R2)
Underdose	5.0E-5	Hypokalemia	1.0E-3	5.0E-8 (R3)

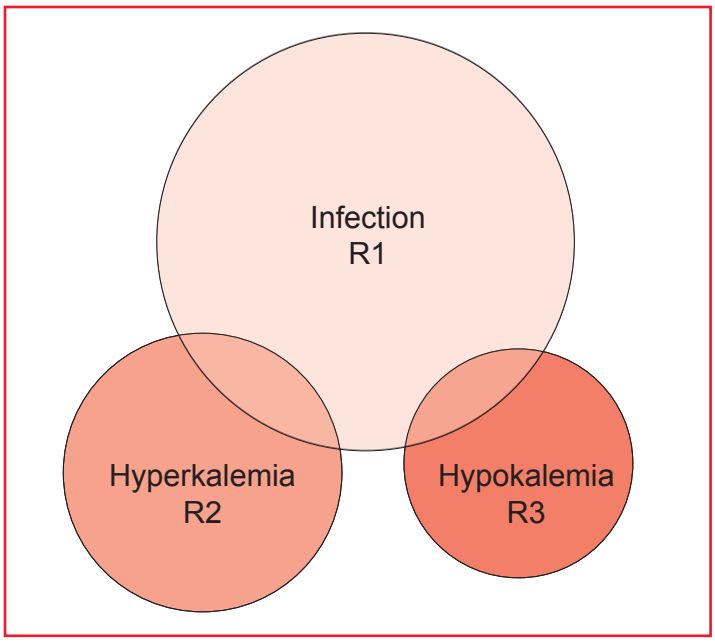

Figure 2 — Risk of Death From All Hazards of the Infusion Pump.

be reduced to acceptable levels is through compliance with applicable and appropriate standards. For example, IEC 60601-1 provides allowable safe limits for leakage current from medical electrical equipment. If it can be shown by objective evidence that the subject device is compliant with an applicable standard, then it can be deduced that risks due to the hazards that are addressed in that standard are acceptable.

For hazards that are not addressed in standards, other methods are used to establish risk acceptability. For devices that are not novel, ISO 14971 provides guidance on methods of establishing risk acceptability criteria. One such method takes into account the state of the art (SOTA) and available information such as technology and practice existing at the time of design of the subject medical device. SOTA is defined in ISO 14971 as "what is currently and generally accepted as good practice" and does "not necessarily mean the most technologically advanced solution."

If a comparable medical device is already approved for commercial use, it can be presumed that its benefits outweigh its risks. In some cases, there may be a pharmaceutical alternative therapy. As with any medical solution, pharmaceutical therapies also have risks and benefits. Similarly, a pharmaceutical alternative therapy to a medical device can also serve as a benchmark for risk acceptability. That is, it can be presumed that its benefits outweigh its risks. Therefore, if the benefit offered by the subject medical device is comparable to the benefit of a currently used medical device, or pharmaceutical therapy option, then the risk of the predicate medical device or the pharmaceutical therapy option can serve as the benchmark for risk acceptability of the subject medical device.

While we can use SOTA as a benchmark of risk acceptability, new technologies that have become available since SOTA should be deployed to reduce risk further. Care should be taken to ensure that the *overall* residual risk does not increase, while individual residual risks are being reduced.

For new and novel devices, acceptability of risk is determined by comparing the benefits of the subject device with the risks that it poses. These benefits are established by valid scientific evidence generated during clinical studies.

ISO 14971:2012

While ISO 14971:2007 allows some flexibility in how, and to what extent, risk/benefit analyses are done, ISO 14971:2012 adds more restrictions through a strict interpretation of EU Directive 93/42/EEC. Under this strict interpretation, risks must be reduced to as low as possible, regardless of economic consequences. Also, risk/benefit analyses must be done for all individual risks, as well as for the overall device.

It can be surmised that if the *overall* residual risk of the device is acceptable, the *individual* residual risks of the device are also acceptable. However, the converse is not necessarily true. That is, it is possible that the individual risks of a device are acceptable, but the overall residual risk is not acceptable.

Techniques for risk/benefit analysis are presented here. The same mechanism for risk/benefit analysis can be used both for individual residual risks and the overall residual risk.

Risk/Benefit Analysis

Once the residual risk is quantitatively computed *and* a numerical risk acceptability basis is established, evaluation of the overall residual risk can follow a logic similar to what is depicted in Figure 3. If the subject device offers more benefit and less risk than the state-of-the-art (SOTA) devices in the market, then it can be surmised that the benefits outweigh the risks. This is represented in the upper left quadrant of Figure 3. If on the other hand, the subject device offers less benefit and more risk, it can be surmised that the risks outweigh the benefits. This is depicted in the lower right quadrant of Figure 3. Less clear are scenarios in which the subject device offers more benefit but also more risk, or reduced benefit at a lower risk. For these scenarios, a qualitative risk benefit analysis is performed.

The FDA offered a guidance document on March 28, 2012 to help with the performance of qualitative risk/benefit analyses (which can be found on www.fda.gov and also by contacting Ruth Fischer at 301-796-5735 or Ruth.Fischer@fda.hhs.gov). This guidance document expects the manufacturer to provide a reasonable assurance of safety and effectiveness by weighing any probable

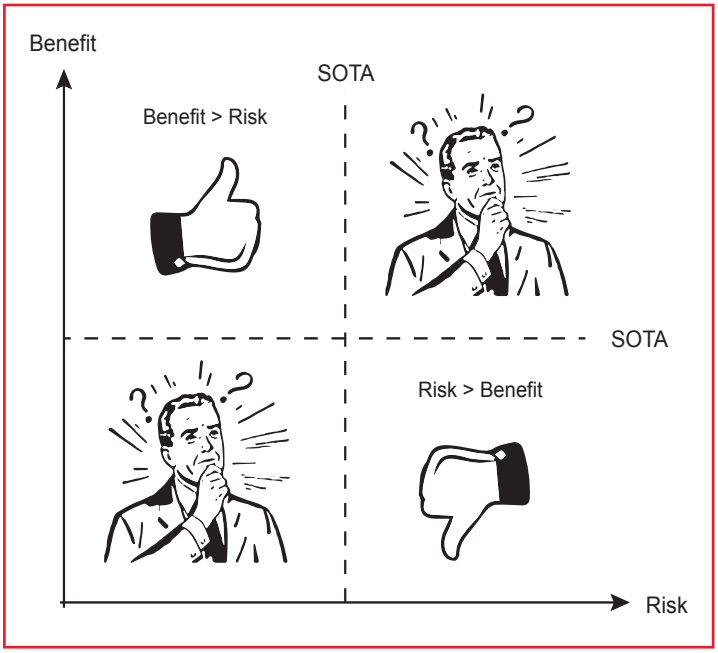

Figure 3 — Risk/Benefit Map.

benefit to health from the use of the device against any probable risk of injury or illness from such use. Examples of types of benefits include:

- Improving quality of life
- Reducing the probability of death
- Reducing the probability of loss of function
- Providing relief from symptoms

Factors that are considered in the qualitative risk/benefit analysis include:

- Quality of clinical data
- Magnitude of the benefit
- Probability of patients receiving the benefit
- Duration of the benefit
- Disease characteristics
  - o Is the disease progressive and degenerative?
  - o How long do patients with the disease live?
  - o How severe is the impact of the disease on patients' lives?
- Value of benefit to patients who receive it
- Patients' understanding of risks and benefits and willingness to accept probable risk of harm, given the probable benefit
- Availability of alternative therapies

Patient's Point of View

A pivotal aspect of risk acceptance is the patient's perspective on the risks and benefits. Given identifiable and definable risks, risk tolerance will vary among patients. Different factors can influence patient risk tolerance, including:

- Severity of disease or condition. Patients suffering from very severe diseases (i.e., those that are life threatening) may tolerate more risk for devices used in treatment. For diagnostic devices, individuals might be more averse to the risk of a false negative result concerning a severe disease.
- Disease chronicity. Some patients with chronic diseases who have adapted to their illness and minimized its interference with their daily lives may tolerate less risk and require risky devices to deliver a greater treatment benefit, whereas other patients who have suffered from a debilitating chronic illness over a long period of time may tolerate higher risk to gain less benefit.
- Availability of alternative treatment/diagnostic options. If there are no other treatment/diagnostic options available, patients may tolerate more risk for even a small amount of benefit.

Conclusion

Despite efforts to objectively and quantifiably weigh the benefits of a medical device against the risks that it poses, this is a fundamentally subjective endeavor. Risk tolerance varies widely from one patient to another and is ultimately an emotional decision. Benefits, on the other hand, can be more objectively measured by clinical studies. Use of existing therapy options as a benchmark of risk acceptance and analytical techniques used to determine the risks of medical devices make it possible to make objective judgments on the risk/benefit balance of medical devices.

About the Author

Bijan Elahi has worked as a risk manager for Class II and Class III medical devices, both in the U.S. and Europe for more than 22 years. He is currently employed at Medtronic, plc and is also a lecturer at Eindhoven University of Technology in Eindhoven, Netherlands, where he teaches risk management to doctoral students in engineering.

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