

## **A Quantitative Framework for Assessing Benefit-Risk in Healthcare Applications**

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### **Author Attribution**

Richard Matt is the sole proprietor at Midwest Consulting in Grayslake, Illinois. Email: richard.matt@mindspring.com Richard has over 30 years' experience with risk management in both product development and remediation for a broad range of medical products, from Class I, II, and III medical devices and combination products. In this time, Richard observed many instances of the need for a more-objective approach to assess whether a product's benefits exceed its risks. The ideas in this paper were developed in response to that need.

### **Disclosure**

A provisional patent (no. 63,461,562) has been issued for the ideas expressed in this paper.

### Abstract

Evidence that the Benefit of a medical procedure exceeds its Risk is fundamental to all branches of medicine. From Hippocrates' "First, do no harm" to the European Union's Medical Device Regulations, the concept that a patient will be helped by a medical procedure more than they will be hurt is the gating medical criteria to a host of events, from releasing new products to the market, to responding to complaints, to judging whether a product should be recalled, to evaluating gaps and improvements to Quality Systems.

Despite the critical importance of showing whether benefit exceeds risk, industry and academia have not found an agreed-upon method. As medicine continues to march forward, this subject has become the topic of increasingly frequent conferences, papers, and research. Unfortunately, these increasing efforts have, to date, merely created more options but no clearly superior approach.

This paper discusses a novel method to determine whether benefit exceeds risk. Most fundamentally, this method separates itself from prior work by establishing a more objective, common metric for measuring both benefits and risks. Another novel element is avoiding the universal mistake of mapping risk to numbers for ease of manipulation. Instead, this method works with the benefit and risk metrics directly, without conversion to numbers and creates a 'risk algebra' to simplify these metrics until it becomes clear whether benefit exceeds risk, or vice versa. This method is unusual in the ease with which it can be applied to any medical procedure, any patient population, and any number or type of risks or benefits. The result is a method to determine whether benefit exceeds risk that is both dramatically more objective than dominant methods and intuitively clear, making conclusions significantly more compelling.

Building on this foundation, over a dozen applications are discussed; e.g., for systematically selecting the best therapy from among a list of alternatives, customizing the Benefit-Risk analysis to small populations or even individuals, and variations on the method's metrics to make traditionally difficult determinations of whether benefit exceeds risk (e.g., for a purely aesthetic purpose) significantly more objective.

*Keywords:* Benefit Exceeds Risk, Benefit/Risk Ratio, Benefit-Risk, benefit:risk, benefit risk, Risk-Benefit, BRA, RBA, Risk Management, Objective, Novel, Risk Algebra, efficacy, safety

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## A Quantitative Framework for Assessing Benefit-Risk in Healthcare Applications

### The Method

#### The Need

The phrase “First, do no harm” is often ascribed to the Hippocratic Oath<sup>1</sup> and is generally recognized as the starting point of ethical medicine. Given the complexities of the human body, it is not always obvious what actions help, and what actions harm, a patient. Therefore, even a goal as modest as “First, do no harm” can be challenging to live up to.

In today’s medical environment, we recognize that every medical product and procedure exposes patients to some amount of risk<sup>2</sup>. With this knowledge, if we focused on ‘patient risk’ without also thinking about ‘patient benefit’, then the combination of “First, do no harm’ and the fact that the use of any medical product or procedure exposes a patient to risk would mean we would do nothing. However, entire point of medicine is that, with the right patient and the right medicine, we *can* do better than ‘doing nothing’. Therefore, to strike a balance that acknowledges the constant presence of both ‘patient risk’ and ‘patient benefit’, the phrase “First, do no harm” can be reasonably revised to “First, ensure the benefits outweigh the risks”.

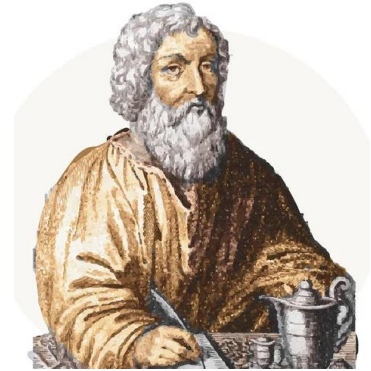


Figure 1 - Hippocrates

Through this reasoning, the idea that the benefits from a medical product or procedure must outweigh its risks has become central to the practice of medicine. The test of whether ‘Benefit exceeds risk’ is central to determining:

- The acceptability of a Quality System or its remediations<sup>3</sup>,
- Product Development Actions<sup>4, 5</sup>:
  - Ethical clinical trials,
  - Whether a product can be legally sold for use on patients,
- Post-market actions<sup>3</sup>:
  - Audit recommendations,
  - Complaint investigations,

<sup>1</sup> Although often attributed to the Hippocratic Oath, this phrase does not appear in the Hippocratic Oath.

<sup>2</sup> The idea that every medical product and procedure exposes a patient to risk will be explored in section “A close look at Patient ‘Benefit’”. For now, note that the Introduction of ISO 14971:2019+A11:2021, *Medical devices - Application of risk management to medical devices* states: “All stakeholders need to understand that the use of a medical device involves an inherent degree of risk, even after the risks have been reduced to an acceptable level.”

<sup>3</sup> Per “Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions”, issued on December 27, 2016, <https://www.fda.gov/media/98657/download>.

<sup>4</sup> Per the FDA’s “Factors to Consider When Making Benefit/Risk Determinations in Medical Device Premarket Approval and De Novo Classifications”, issued Aug. 30, 2019, “This guidance document explains the principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain medical devices.”

<sup>5</sup> Per the EU’s “REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL”, ANNEX I - GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - CHAPTER I - GENERAL REQUIREMENTS, Section 2: “The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.”

- Field actions (including recalls),
- Whether to shut a company down, and
- Product liability lawsuits.

### The Current State

If we define the likely amount of patient benefit of a medical device or procedure as  $B$  and the likely amount of patient risk of a medical device or procedure as  $R$ , then the statement that benefit exceeds risk can be written as:

$$B > R$$

*Equation 1*

Ironically, despite the long-standing requirement from both FDA and EU requiring medical manufacturers to show Equation 1 is true, we have yet to develop an objective and structured approach to show that a product or procedure's benefit exceeds its risk<sup>6</sup>.

1. On the 'risk' side of the equation, we have developed sophisticated tools to help us understand and measure 'risk' and have spent millions of hours training people how to use these tools effectively. For a small sampling of the tools that have helped us understand risk, I will mention:
  - Failure Mode Analysis (FMA)<sup>7</sup>, originating during WWII,
  - Fault Tree Analysis (FTA), originating during the 1960s, and
  - Risk Prediction for Surgery, <http://www.riskprediction.org.uk/>, with elements from 2016.
2. On the 'benefit' side of the equation, we have, unfortunately, not made similar advances:
  - There are no methods for measuring benefit that are analogous to FMEA, FTA, Risk Prediction, etc.
    - The closest thing to a universal metric for benefit is 'financial units' (e.g., Dollars, Euros, Yen, etc.). However, this metric is not suited to medicine because Regulators want the patient's welfare, and not finances, to be the focus of risk management.
  - In contrast to 21 C.F.R. § 820.30(b)-(f)<sup>8</sup>, which requires device manufacturers to establish and maintain procedures on risk analysis, there are no regulatory requirements to establish or maintain procedures on benefit analysis.
3. Regarding our ability to decide whether 'benefit' or 'risk' is larger:
  - In most Benefit-Risk analyses, the benefit and risk are stated in independent and unrelated manners, e.g., in the FDA Guidance<sup>3</sup> on Benefit-Risk analysis, the statements regarding risks and benefits discuss completely different topics, with no obvious way to compare them. Example 1 of this guidance discusses "aesthetic device". The benefit for

<sup>6</sup> *Quantitative Benefit–Risk Assessment: State of the Practice Within Industry*, Meredith Y. Smith, et. al, *Ther Innov Regul Sci.* 2021; 55(2): 415–425. Published online 2020 Oct 27. doi: 10.1007/s43441-020-00230-3

<sup>7</sup> FMA was later expanded to include the effects of a failure mode, as which time the acronym FMA was lengthened (to reflect the additional analysis scope) to FMEA (Failure Mode Effects Analysis).

<sup>8</sup> Per 21 C.F.R. § 820.30(b)-(f): Device manufacturers must "establish and maintain procedures for validating the device design," which must "include software validation and risk analysis, where appropriate."

this device is simply stated as “moderate,” with “some patients . . . [seeing] long-term aesthetic improvement” and the risks were stated as “adverse events of varying severity.” These statements have no obvious way to be compared, making it difficult to defend statements that benefit exceeds risk or vice versa.

- Some progress has been made measuring both benefit and risk with the metric “change to the patient’s lifespan”<sup>9</sup>. While this example does use the same metric to measure both benefit and risk, there are also significant problems that the method in this paper will overcome:
  - We can not measure the benefit and risk of a medical product or procedure by measuring changes in the patient’s lifespan for risks and benefits that do not impact the patient’s lifespan in a measurable manner; e.g., changes in the patient’s lifespan are unlikely to be useful for acute-care medical products or procedures, and
  - The second significant problem is that, even for those medical conditions that *do* impact a patient’s lifespan, measuring this effect will, necessarily, take years to decades. This will dramatically increase the cost of risk management at a time when we have not demonstrated a need to dramatically increase the cost of risk management.
- The Quality-Adjusted Time without Symptoms and Toxicity<sup>10</sup> is another method that uses the same metric to measure both benefit and risk, where the metric is the time lost due to a medical treatment subtracted from the time gained from the treatment<sup>11</sup>. While this example uses the same metric to measure both benefit and risk, and since this example avoids the problem of requiring a statistically significant change in the patient’s lifespan, the same problems exist for “Quality-Adjusted Time without Symptoms and Toxicity” as they did for the previous ““change to the patient’s lifespan”, but to a smaller degree.
- Incremental net health benefit (INHB)<sup>10</sup> is similar to Quality-Adjusted Time without Symptoms and Toxicity.
- Multi-Criteria Decision Analysis (MCDA)<sup>10</sup> is a tool to support decision-making where several benefits and risks can be taken into account. This method is based on hierarchical decision trees that include defined options with different probabilities of occurrence. This approach is promising as it identifies which areas (risks or benefits) are more influential and need more scrutiny; however, the model can be quite complex and statistically tricky, and the assigned weights can bring bias of subjectivity into the model.

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<sup>9</sup> *The new Sheffield risk and benefit tables for the elderly*, QJ Med 2011; 104:3-12 measures both the risk to a patient’s life from cardiovascular disease as a reduction in their expected lifespan and measure the benefit to a patient’s life from taking a drug to treat cardiovascular disease.

<sup>10</sup> *Assessing the benefit:risk ratio of a drug - randomized and naturalistic evidence*, Dialogues Clin Neurosci. 2011 Jun; 13(2): 183–190.

<sup>11</sup> *The new Sheffield risk and benefit tables for the elderly*, QJ Med 2011; 104:3-12 measures both the risk to a patient’s life from cardiovascular disease as a reduction in their expected lifespan and measure the benefit to a patient’s life from taking a drug to treat cardiovascular disease.

- Some progress has been made measuring both benefit and harm with the metric “Number-Needed-to . . .”<sup>12</sup>, as in “Number-Needed-to Treat (NNT)” and “Number-Needed-to-Harm (NNH). While this example does use the same “Number-Needed-to . . .” metric for benefit and harm, the method identifies only the probabilities of harm or benefit and not severity. Therefore, this method doesn’t measure ‘risk’ and fails as a technique that uses the same metric for both benefit and risk.
- While filing a 510(k) submission to “demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device”<sup>13</sup>, manufacturers traditionally show whether their product’s benefit exceeds its risk by using ‘equivalence tables’ to show that their product’s safety and efficacy (aka ‘risks’ and ‘benefits’) is at least as good as a “predicate device” that the manufacturer has identified because the “predicate device’s” safety and efficacy record is both well-established and accepted by regulatory bodies. By choosing a predicate device with an accepted benefit and risk and by showing that the manufacturer’s device is at least as good as the predicate device, the manufacturer shows the benefit and risk of the device in the 510(k) is also acceptable.
  - The first problem with this submission strategy is that it requires a similar product already exist.
  - While unusual, the second problem is that regulators occasionally remove products that have been on the market for years<sup>14</sup>. This practice will throw into question all 510(k) approvals using this product in an equivalence table.
  - In contrast, the method to show benefit exceeds risk in this paper can be used on both completely novel medical products or, or on elements of an existing medical product design that are novel without the risk that changes in another product’s regulatory status will impact your product’s status.

In summary, “In the last decade there has been a significant increase in the literature discussing the use of benefit–risk methods in medical product (including devices) development. Government agencies, medical product industry groups, academia, and collaborative consortia have extensively discussed the advantages of structured benefit–risk assessments. However, the abundance of information has not resulted in a consistent way to utilize these findings in medical product development.”<sup>15</sup> Existing approaches to show benefit exceeds risk have significant drawbacks, including excessive appeal to expert opinion (lack of objective standards), potentially waiting for decades to collect data, not applying to novel products or procedures, and being overturned by changes in the regulatory status of other products. Without a universal, structured approach that enables objective comparisons of benefit and risk for any product, it is impossible to consistently and confidently state whether the risks or benefits of a medical treatment are greater.

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<sup>12</sup> *The NNT, Explained*, 2022, <https://thennt.com/thennt-explained/>

<sup>13</sup> Section 513(i)(1)(A) of the Food, Drug, and Cosmetic (FD&C) Act

<sup>14</sup> Reuters, Sept. 12, 2023, *US FDA panel says popular decongestant used in cold medicines ineffective*, <https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-panel-says-popular-decongestant-used-cold-medicines-ineffective-2023-09-12/>

<sup>15</sup> Per “*Global Landscape of Benefit–Risk Considerations for Medicinal Products: Current State and Future Directions*”, *Pharmaceutical Medicine*, volume 36, pages201–213 (2022), 03 July 2022



The method in this paper *is* a universal, structured approach that significantly improves the objectivity of Benefit-Risk analysis while also overcoming the shortcomings of prior methods.

### Moving to a Future State – A close look at Patient ‘Benefit’

The FDA’s definition of a patient is “Any individual with or at risk of a specific health condition, whether or not he or she currently receives any therapy to prevent or treat that condition. Patients are the individuals who directly experience the benefits and harms associated with medical products”.<sup>16</sup> This definition of a patient has two parts (“Any individual with a specific health condition” and “Any individual at risk of a specific health condition”) that align with therapeutic, or diagnostic and preventive medical care.

- 1) The medical benefits and risks of a therapeutic medical product or procedure are fairly self-evident: The benefit of the medical product or procedure is that the health condition is improved – either partially or fully. The risk of the medical product or procedure is that it might cause some new harm (e.g., an infection) or that the health condition’s improvement is not as extensive as usual.
- 2) The medical benefits of a diagnostic medical product or procedure are also fairly self-evident – the presence or absence of a health condition is accurately identified. However, the scope of risks for a diagnostic medical product or procedure are more subtle. Not only is there the chance that a diagnostic product or procedure might cause some new harm (e.g., an infection), but there are the additional risks of not reporting a health condition that is present and reporting a health condition that is not present. This last option can lead to still more risks: a) Performing an unnecessary therapeutic procedure, or b) To avoid performing unnecessary therapeutic procedures, performing additional diagnostic tests. And, even if additional diagnostic procedures eventually sort out the proper diagnostic result, this can result in months of therapeutic delays as successive conflicting diagnostic results are resolved to reach a single, confirmed result.
- 3) The medical benefits and risks of a preventative medical product mirror exactly the benefits and risks of a therapeutic product. The benefit of the medical product or procedure is successfully avoiding the undesirable health condition – either partially or fully. The risk of the medical product or procedure is that it might cause some new harm or that the health condition occurs despite the preventative medical product.

Thus, whether the purpose of a medical treatment is therapeutic, diagnostic, or preventative<sup>17</sup>, every medical treatment exposes the patient to risks<sup>2</sup>. Or, restating the previous sentence with equations, for every medical treatment,  $R > 0$ .

Since  $R > 0$  for every medical treatment, and, per Equation 1,  $B > R$  for an ethical medical product or procedure, then the amount of benefit a patient is expected to receive from a medical treatment holds a very special role in medicine:

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<sup>16</sup> Per the “Patient-Focused Drug Development Glossary”, <https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary#:~:text=Patient%3A%20Any%20individual%20with%20or,harms%20associated%20with%20medical%20products>

<sup>17</sup> The term ‘medical treatment’ shall be understood to include therapeutic, diagnostic, and preventative medical products and procedures.

## ASSESSING BENEFIT-RISK

*The likely 'benefit' of a medical treatment establishes an upper limit on the likely amount of 'risk' that a patient can ethically be exposed to from the medical treatment; i.e.,  $B > R$ .*

If we now define  $H$  as the likely amount of harm from a specific health condition, then  $H \geq B$  because a medical treatment:

- can not improve (or 'benefit') the patient's health by more than the amount of harm caused by a specific health condition; i.e.,  $H$  is the maximum possible value for  $B$ , or  $H = B$ .
- may improve the patient's health,  $B > 0$ , without completely curing us, so  $H > B$ .

Therefore, the definition of  $H$  means that:

*The likely 'harm' of a medical condition establishes an upper limit on the likely amount of 'benefit' that a patient can ethically be exposed to from the medical treatment; i.e.,  $H \geq B$ .*

If we now consider someone who does not meet the FDA's definition of a patient, that person *simultaneously* does not currently have a health condition *and* is not at risk of a health condition in the future; i.e., for this person,  $H = 0$ . We will refer to this person as '100% healthy' and everyone who *meets* the FDA's definition of a patient will be referred to as '<100% healthy'.

Since  $H \geq B$  and  $B > R$ , then, by the transitive properties of inequalities,  $H > R$ . Therefore, when  $H = 0$ , it must also be true that both  $B = 0$  and  $R = 0$  for an ethical medical treatment. However, as we



Figure 3 - Available Benefit and Risk for a 100% Healthy Person

discussed at the start of this section, every medical treatment exposes the patient to some risk; i.e.,  $R > 0$  for every medical treatment. Since  $R > 0$  for every medical treatment, but  $R = 0$  for an ethical medical treatment, then we can reach the conclusion that it is not ethical to perform a medical treatment on anyone for whom  $B = 0$ .

On the other hand, per **Error! Reference source not found.**, if someone either has, or is at least at risk of, a health condition, then their health is less than 100% (e.g., 90% in **Error! Reference**



Figure 2 - Available Benefit and Risk for a 90% Healthy Person

**source not found.**) This loss of health presents an opportunity for the patient to benefit from a medical treatment. We can, then, ethically expose this person to a medical treatment if that medical treatment's expected risk is less than the treatment's expected benefit.

[A real-world example of benefit and risk tradeoffs](#)

If you live in the United States, you may have seen recent television ads about using Botox to treat migraines<sup>18, 19</sup>. The ads state that Botox *is intended* to treat migraines in people with at least 15 headache days per month, where each headache lasts 4 hours a day or longer; i.e.,  $H =$  "at least 15 headache days per month, where each headache lasts at least 4 hours a day". Since  $H \geq B$  and  $B > R$ , then, by the transitive properties of inequalities,  $H > R$ . If we assume that, in order to maximize their patient population, that Botox set  $H$  as low as possible while still exceeding  $R$ , then  $R$  is only slightly smaller than  $H$ , so that  $R \approx$  "15 headache days per month, where each headache lasts 4 hours a day". This enables us to infer, from the symptoms necessary for a patient to meet the intended use, that the medical treatment of migraines with Botox can be expected to cause significant, harmful side-effects.

By extension, as the patient's health condition becomes more dire (i.e., as the amount of potential benefit increases), the amount of risk that we can tolerate in procedures that treat the patient's health condition also increases. In the limit, patients with extreme health conditions (including terminally ill patients) may legally and ethically be given experimental medical treatments with unproven risks and benefits<sup>20</sup>, typically through either controlled trials or compassionate use programs.

Over the course of the next four sections, we will leverage this section's look at 'benefit' to develop a more objective method of determining whether benefit exceeds risk.

### Moving to a Future State – Describing 'Benefit' with 'Risk'

Since  $H$  is the likely amount of harm from a specific health condition, then, using the definition of  $B$  from before Equation 1, we can see that  $H - B$  is the likely amount of harm from the health condition that remains *after* the medical treatment; i.e., the benefit from a medical treatment is the same as the reduction in the patient's health condition from a medical treatment.

By itself, the last sentence just says the same thing twice, but with different words. However, when we juxtapose a paraphrased definition of risk from ISO 14971<sup>21</sup> with definition of  $H$  from this document, we get:

- 'risk'<sup>22</sup> is a 'combination of the probability of occurrence and severity of a specific harm', and
- $H$  is the likely amount of harm from a specific health condition.

Comparing these two statements, we can see that  $H$  is an estimate of the likely amount of harm from a specific health condition, and 'risk' is a probabilistic (aka 'likely') estimate of the severity (aka 'amount') of harm from a specific harm (aka 'health condition'). This comparison enables us to state that  $H$  is the risk to someone's health from their health condition.

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<sup>18</sup> Voice Over for "Botox for Chronic Migraine" National TV Spot, <https://www.facebook.com/watch/?v=296669711259970>

<sup>19</sup> Botox Injections for Migraine Treatment, Susan Bernstein, 2022, <https://www.webmd.com/migraines-headaches/botox-migraines>

<sup>20</sup> *An analysis of common ethical justifications for compassionate use programs for experimental drugs*, BMC (BioMedical Central) Medical Ethics, 2016, Vol. 17, Article 60.

<sup>21</sup> ISO 14971:2019+A11:2021, Medical devices - Application of risk management to medical devices

<sup>22</sup> The exact definition for 'risk' in ISO 14971 is a "combination of the probability of occurrence of *harm* and the *severity of that harm*".

The significance of showing that  $H$  is a 'risk' to someone's health is that this realization enables us to use the well-established tools that were developed for estimating the size and likelihood of risk from a medical device in the novel application of estimating the size and likelihood of benefit from a health condition. Similar to  $H$  being the risk from a specific health condition,  $H - B$  is the risk that remains from a health condition *after* the medical treatment is completed.

We can not directly observe the benefit of a medical treatment. What we *can* observe is the patient's health condition before and after a medical treatment, and we can compare the two observations to infer the benefit of a medical treatment. In order to define our directly observed quantities, we shall define:

$R_B$  as the likely amount of risk from the patient's health condition **B**efore the medical treatment, and

$R_A$  as the likely amount of risk from the patient's health condition **A**fter the medical treatment, then:

$$R_B = H,$$

$$R_A = H - B, \text{ and}$$

$$R^B = \{(P_1^B, S_1^B), (P_2^B, S_2^B), (P_3^B, S_3^B), \dots, (P_m^B, S_m^B)\}$$

$$R^A = \{(P_1^A, S_1^A), (P_2^A, S_2^A), (P_3^A, S_3^A), \dots, (P_m^A, S_m^A)\}$$

$$B = R_B \overset{\sim}{\sim} R_A$$

$$B \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R_A \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R \cup R_A$$

Equation 2

We have now defined three variables about risk:  $R_B$ ,  $R_A$ , and  $R$ . In order to clarify the similarities and differences among these three definitions, we will use the following IS/IS-NOT matrix:

Characteristic	$R_B^{23}$		$R_A^{24}$		$R^{25}$	
	IS	IS NOT	IS	IS NOT	IS	IS NOT
Represents Patient Risk	X		X		X	
Represents Risk for the Patient Population	X		X		X	
Represents Risk for the Indications for Use		X		X	X	
Represents Risk for Contraindicated Uses		X		X		X
Represents Unmitigated Risk		X		X		X
Represents Mitigated Risk	X		X		X	
Represents Risk for Expected Misuse		X		X	X	
Represents Risk for Unexpected Misuse		X		X		X
Represents Individual Residual Risks, per the definition of 'Residual Risk' in ISO 14971		X		X	X	
Represents Risk from the Patient's Health Condition <u>B</u> efore the Medical Treatment	X			X		X
Represents Risk from the Patient's Health Condition <u>A</u> fter the Medical Treatment		X	X			X

<sup>23</sup> Right before  $R^A = \{(P_1^A, S_1^A), (P_2^A, S_2^A), (P_3^A, S_3^A), \dots, (P_m^A, S_m^A)\}$

$$B = R_B \overset{\sim}{\sim} R_A$$

$$B \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R_A \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R \cup R_A$$

Equation 2, we defined  $R_B$  as the likely amount of patient risk from the patient's health condition **B**efore the medical treatment.

<sup>24</sup> Right before  $R^A = \{(P_1^A, S_1^A), (P_2^A, S_2^A), (P_3^A, S_3^A), \dots, (P_m^A, S_m^A)\}$

$$B = R_B \overset{\sim}{\sim} R_A$$

$$B \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R_A \overset{\sim}{\sim} R$$

$$R_B \overset{\sim}{\sim} R \cup R_A$$

Equation 2, we defined  $R_A$  as the likely amount of patient risk from the patient's health condition **A**fter the medical treatment.

<sup>25</sup> Right before Equation 1, we defined  $R$  as the likely amount of patient risk from the medical treatment.

Characteristic	$R_B^{23}$		$R_A^{24}$		$R^{25}$	
	IS	IS NOT	IS	IS NOT	IS	IS NOT
Represents <u>R</u> isk from the Medical Treatment		X		X	X	
Represents <u>R</u> isk from Side-Effects of the Medical Treatment		X		X	X	

Table 1 - - IS / IS-NOT Matrix for  $R_B$ ,  $R_A$ , and  $R$

Moving to a Future State – Establishing a Common Metric

An important feature of the definitions for Equation 1 and  $R^A = \{(P_1^A, S_1^A), (P_2^A, S_2^A), (P_3^A, S_3^A), \dots, (P_m^A, S_m^A)\}$

$$B = R_B \overset{\sim}{=} R_A$$

$$B \overset{\sim}{>} R$$

$$R_B \overset{\sim}{=} R_A \overset{\sim}{>} R$$

$$R_B \overset{\sim}{>} R \cup R_A$$

Equation 2 is that  $R_B$ ,  $R_A$ , and  $R$  describe risks to the patient’s health. Therefore, if we establish an appropriate metric for risk to patient health, we will have the means to achieve the well-known goal<sup>26</sup> of measuring both benefit and risk with the same metric. This is important because it enables us to directly compare the amount of risk and the amount of benefit in a significantly more objective manner than has traditionally been done for medical devices; i.e., we can show whether Equation 1,  $B > R$ , is true or not in a significantly more objective manner.

There are a few, simple requirements for an appropriate risk metric. It must:

1. Measure every possible risk to a patient’s health, including:
  - a. The smallest possible risk,
  - b. The largest possible risk,
  - c. Being continuous; i.e., not have any gaps where risk is not measured.
2. Produce only one measurement result for a given patient risk; i.e., increase monotonically.
3. Produce different measurement results for different risks.
4. Be as objective as possible.
5. Use the same metric to measure all risks.

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<sup>26</sup> Section 3 of *Translating the Dose Response into Risk and Benefit*, John B. Warren, British Journal of Clinical Pharmacology, Oct. 2019

Fortunately, the task of measuring risk has already been carefully considered and one possible solution is provided in ISO 14971<sup>21</sup> and TR 24971<sup>27</sup>.

Per section 3.18 of ISO 14971, risk is a combination of severity and probability<sup>28</sup>; i.e.,

$$R_i = (P_i, S_i)$$

Equation 3

Where:  $R_i$  is the  $i^{th}$  risk,

$P_i$  is the probability of harm from the  $i^{th}$  risk,

$S_i$  is the severity of harm from the  $i^{th}$  risk, and

$(P_i, S_i)$  is an ordered pair that holds  $P_i$  and  $S_i$ .

Tables 4 and 5 of TR 24971 expands on Section 6 of ISO 14971, 'Risk Evaluation', to present the following tables<sup>29</sup>, which resolve the entire range of risk to five categories for Severity and five categories for Probability:

Common Terms	Possible Description
Catastrophic / Fatal	Results in death
Critical	Results in permanent impairment or irreversible injury
Serious / Major	Results in injury or impairment requiring medical or surgical intervention
Minor	Results in temporary injury or impairment not requiring medical or surgical intervention
Negligible	Results in inconvenience or temporary discomfort

Table 2 - Example of five qualitative **severity** levels

Common Terms	Examples of Probability Range
Frequent	$\geq 10^{-3}$
Probable	$< 10^{-3}$ and $\geq 10^{-4}$
Occasional	$< 10^{-4}$ and $\geq 10^{-5}$
Remote	$< 10^{-5}$ and $\geq 10^{-6}$
Improbable	$< 10^{-6}$

Table 3 - Example of five semi-quantitative **probability** levels

<sup>27</sup> ISO/TR 24971:2020, Guidance on the application of ISO 14971

<sup>28</sup> The following nomenclature is critical to understanding the metric for risk.

<sup>29</sup> While non-table-based risk metrics can be created to measure both benefit and risk, this paper will discuss only table-based risk metrics.

The third requirement for a risk metric, *Produce different measurement results for different risks*, is not strictly met for Table 2 and Table 3 because the categories for Severity and Probability are so wide that lots of different risks will have the same metric. However, the thinner the categories, the more data is required to determine the proper category to properly categorize a risk. Table 2 and Table 3 are the result of compromise by the Technical Committee that wrote ISO 14971 between the amount of data needed to discern in which category a risk belongs and the ability of Table 2 and Table 3 to resolve differences between risks.

Table 2 and Table 3 were designed to measure the risks from the medical treatment; i.e., the risks in  $R$ . For this reason, Table 3 doesn't resolve risks that occur more frequently than 0.1% of the time. However, since the risks in of  $R_B$  represent the patient's risks to health before treatment, at least some of the risks in of  $R_B$  will always occur. Therefore, some of the risks in  $R_B$  will occur significantly more often than 0.1% of the time. Therefore, if we use Table 3 as a risk metric, we will measure significantly different risks as the same if the risks that occur more often than 0.1% of the time. This fails the requirement to *Produce different measurement results for different risks* significantly more than for other probabilities of risk.

In order to correct our risk metric to treat risks with high rates of occurrence the same as risks for lower rates of occurrence, we first note that Table 3 uses decade-wide ranges for the center three risk categories. Therefore, we will extend the high-occurrence end of Table 3, while maintaining consistency with decade-wide probability ranges in the center of Table 3. The result is:

Common Terms	Examples of Probability Range	Equivalent Statements of Probability	
Expected	$\geq 10^{-0}$ and $\geq 10^{-1}$	$\geq 1.0$ and $\geq 0.1$	$\geq 100\%$ and $\geq 10\%$
Often	$< 10^{-1}$ and $\geq 10^{-2}$	$< 0.1$ and $\geq 0.01$	$< 10\%$ and $\geq 1\%$
Frequent	$< 10^{-2}$ and $\geq 10^{-3}$	$< 0.01$ and $\geq 0.001$	$< 1\%$ and $\geq 0.1\%$
Probable	$< 10^{-3}$ and $\geq 10^{-4}$	$< 0.001$ and $\geq 0.0001$	$< 0.1\%$ and $\geq 0.01\%$
Occasional	$< 10^{-4}$ and $\geq 10^{-5}$	$< 0.0001$ and $\geq 0.00001$	$< 0.01\%$ and $\geq 0.001\%$
Remote	$< 10^{-5}$ and $\geq 10^{-6}$	$< 0.00001$ and $\geq 0.000001$	$< 0.001\%$ and $\geq 0.0001\%$
Improbable	$< 10^{-6}$	$< 0.000001$	$< 0.00001\%$

Table 4 - Expanded Quantitative Table of Probability

Table 2 can also be challenged for improvements; e.g., in the 'Application' section of this paper:

1. Two of the five categories in Table 2 briefly discuss 'time'. The section of this paper titled "*Accounting for Time-Varying Benefits and Risks*" discusses an alternative way of accounting for the effect of 'time' on risk and may cause the references to 'time' in Table 2 to be changed.
2. When most people read the categories in Table 2, they are thinking of physical harm to the patient. However, some medical products are designed to mitigate mental or emotional harm to the patient; e.g., drugs to improve a patient's mental state or surgeries for aesthetic reasons only to improve a patient's sense of wellbeing. The section of this paper titled "Customizing Risk Metrics for Risks for Emotion" discusses a possible process to change Table 2 to account for these factors.

Despite the opportunity to create many other metrics, in this paper, we will use Table 2 to measure the severity of risk and Table 4 to measure the probability of risk.



Now that we've established that risk metrics that are suitable to measure both the benefits and risks of a medical treatment, we will now discuss how to organize all of the risks in  $R_B$ ,  $R_A$ , or  $R$  so that simplifying Equation 1 becomes straightforward.

### Moving to a Future State – Organizing Risks

If we use  $R^A = \{(P_1^A, S_1^A), (P_2^A, S_2^A), (P_3^A, S_3^A), \dots, (P_m^A, S_m^A)\}$

$$B = R_B \cup R_A$$

$$B \succ R$$

$$R_B \cup R_A \succ R$$

$$R_B \succ R \cup R_A$$

Equation 2 to substitute  $R_B$  and  $R_A$  into Equation 1, and if we add  $R_A$  to each side of the equation, then we get a particularly useful equation:

$$R_B > R_A + R$$

Equation 4

Please note that:

- the left-hand side of Equation 4 represents the patient's risk total *before* a medical device is used to treat their health condition, and
- the right-hand side of Equation 4 represents the patient's risk total *after* a medical device is used to treat their health condition; i.e., the component of risk from the health situation that remains after the medical treatment and the component of risk from the medical treatment.

Therefore, Equation 4 states that the patient risk before a medical device is used to treat their health condition must be greater than the patient risk after that medical device is used to treat their health condition.

While Equation 4 looks familiar to anyone who uses inequalities with real numbers, the three variables in Equation 4,  $R_B$ ,  $R_A$ , and  $R$ , represent 'sets of risks' and not 'real numbers'. While the following substitutions will look reasonable to many readers, those readers who are familiar with abstract algebra can verify the technical correctness of the substitutions:

- The 'addition sign', '+', for real numbers is replaced by the 'union sign', 'U', for sets, and
- The greater than sign, '>', for real numbers is replaced by a 'greater risk sign', ' $\succ$ ', for sets of risks. Just like '>' indicates that the number on the left-hand side of the inequality is larger than the number on the right-hand side of the inequality, ' $\succ$ ' indicates that the total amount of risk on the left side of the inequality is greater than the total amount of risk the right side of the inequality.

With these substitutions, Equation 4 becomes:

$$R_B \overset{\sim}{\supset} R_A \cup R$$

Equation 5

The three terms in Equation 5 each represent a set of risks, where, per Equation 3, each risk is represented by an ordered pair whose abscissa is the probability of harm and the ordinate is the severity of harm.

We will now use Equation 5 to describe a useful and, for many, a familiar way to organize risks: Figure 4 of TR 24971 presents the following table to organize the risks to a patient from the medical treatment:

		Qualitative <b>severity</b> levels				
		Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Semi-quantitative <b>probability</b> levels	R					
	Frequent					
	Probable	$R_1$	$R_2$			
	Occasional		$R_4$		$R_5$	$R_6$
	Remote					
Improbable			$R_3$			

Table 5 - Example of a semi-quantitative 5 x 5 risk matrix

Since the previous table is based on the five probability categories in table 5 from TR 24971, and since, for Benefit-Risk Analysis, we will use the seven probability categories in Table 4 from this paper to measure the probability component of patient risk, we will extend table 5 from TR 24971 by adding two more probability categories. The result is the following table, which we shall use extensively in this paper:

		Qualitative <b>severity</b> levels				
		Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Semi-quantitative <b>probability</b> levels	R					
	Expected					
	Often					
	Frequent					
	Probable					
	Occasional					
	Remote					
Improbable						

Table 6 - Example of a semi-quantitative 7 x 5 risk matrix

Per the definition of  $R$  (right before Equation 1) and the right-most two columns of Table 1,  $R$  represents the residual risks, as discussed in ISO 14971. If we say the medical device will present  $n$  risks to the patient (where  $n$  can represent any integer greater than zero<sup>2</sup>), then we can represent the set of risks in  $R$  any of three ways:

1. Using  $n$  discrete risks, we can represent  $R$  as  $\{R_1, R_2, R_3, \dots, R_n\}$  (as was done in Figure 2 of TR 24971).

2. Starting with  $n$  discrete risks, we can use Equation 3 to expand how we represent the set of  $n$  discrete risks in  $R$  from  $\{R_1, R_2, R_3, \dots, R_n\}$  to  $\{(P_1, S_1), (P_2, S_2), (P_3, S_3), \dots, (P_n, S_n)\}$ .

For example, if we have a medical treatment that exposes the patient to six risks and if

$$R = \left\{ (Frequent, Minor), (Occasional, Critical), (Serious / Major, Improbable), (Occasional, Critical), (Remote, Catastrophic), (Probable, Negligible) \right\}$$

Equation 6

then populating Table 6 with  $R$  results in:

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected					
Often					
Frequent		( <i>Frequent</i> , <i>Minor</i> )			
Probable	( <i>Probable</i> , <i>Negligible</i> )				
Occasional				( <i>Occasional</i> , <i>Critical</i> ), ( <i>Occasional</i> , <i>Critical</i> )	
Remote					( <i>Remote</i> , <i>Catastrophic</i> )
Improbable			( <i>Improbable</i> , <i>Serious / Major</i> )		

Table 7

3. If we Replace the contents of each cell in Table 7 by a ‘count’ of the number of risks that appear in that cell, so Table 7 becomes Table 8, shown below<sup>30</sup>:

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	1	0	0	0
Probable	1	0	0	0	0
Occasional	0	0	0	2	0
Remote	0	0	0	0	1
Improbable	0	0	1	0	0

Table 8 – Representing the Set of Risks in  $R$  in a Table Format

Just as we used Table 8 to represent the set of risks in  $R$ , we will use similar tables to represent the sets of risks in  $R_B$  and  $R_A$ .

<sup>30</sup> Many Risk Management systems that follow ISO 14971 will create a table like Table 8 to summarize a product’s individual residual risks.

By substituting the tables that contain  $R_B$ ,  $R_A$ , and  $R$  into Equation 5, we get a ‘table version’ of Equation 5:

$$Table_{R_B} \gtrsim Table_{R_A} \cup Table_R$$

We can simplify the right-hand side of the previous equation as follows:

$$Table_{R_A} \cup Table_R = Table_{R_A \cup R}$$

Equation 7

with standard matrix addition; i.e., by adding the risk count in corresponding cells of  $Table_{R_A}$  and  $Table_R$  and putting the sum into the same cell in  $Table_{R_A \cup R}$ .

With this simplification, Equation 5 becomes Equation 8, below:

$$Table_{R_B} \gtrsim Table_{R_A \cup R}$$

Equation 8

Or, in table form,

$R_B$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected					
Often					
Frequent					
Probable					
Occasional					
Remote					
Improbable					

}

$R_A \cup R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected					
Often					
Frequent					
Probable					
Occasional					
Remote					
Improbable					

Equation 9

where:

- Each table in Equation 9 represents a set of risks (the set  $R_B$  on the left-hand side of Equation 9 and the set  $R_A \cup R$  on the right-hand side of Equation 9),
- Each cell in each table in contains a ‘count’ of the number of risks with that cell’s combination or probability and severity, and
- Each count is obtained by the process shown above to use Table 7 to obtain a count in Table 8 of the risks in Equation 6.

Implementation

Equation 9 is the culmination of our application of Equation 1,

$$B > R$$

Equation 1

Attachment A explains four rules of a ‘risk algebra’ that can be used to simplify Equation 9 until it is intuitively obvious whether it is true or not. Because these rules are designed to not change whether the inequality in Equation 9 is true or not, if the simplified version of Equation 9 is true, then Equation 1 is true; i.e., the benefit of the medical treatment outweighs the risks.

Attachment B contains two examples of the process, from start to finish, of applying the method in this paper to determine whether the benefit of a medical treatment outweighs the risks. Both examples use the same medical treatment - a blood transfusion. The first example uses the patient population of people who arrive at an ER with bleeding ulcers and who meet the site's protocol for needing a blood transfusion. The second example uses a slightly different patient population – all people who arrive at an ER with bleeding ulcers, including those that do not meet the site's protocol for needing a blood transfusion.

- In the first example, the method in this paper affirms that the site's protocol for transfusing patients with bleeding ulcers by concluding that the benefits of a blood transfusion exceed the risks.
- In the second example, the method in this paper concludes that, for the larger population of all patients with bleeding ulcers, including those who do not meet the site's protocol for needing a blood transfusion, the risks of a blood transfusion outweigh the benefits.

In short, the method in this paper concurs with current practice at an ER to both give, and to not give, patients with bleeding ulcers a blood transfusion.

Because this paper's method of determining whether the benefit of a medical treatment exceeds the risk has many advantages that are not immediately obvious, Attachment C contains a few unexpected examples of applications of the method in this paper. For example, estimates of risk based on ISO 14971 are useful to compare the relative size of various risks, but there is no meaning to the absolute size of these risks. This paper's method changes that completely. By using values of risk to determine if Equation 1 is true, the equation *gives meaning* to the absolute value of the risks. The absolute value of treatment risks now has meaning – and the meaning is to show whether the absolute value of the treatment risk is larger or smaller than the absolute value of the benefit to a patient's health condition. That the absolute value of Risk now has meaning is a fundamental change in Risk Management, and the applications of this method reflect the new opportunities that are now available because of this fundamental change.

## Conclusion

The result of this paper is the development and presentation of a structured, universal approach to assessing the Benefit-Risk Analysis of any medical treatment. This method has the advantages that it:

- Can incorporate multiple harms and benefits into the Benefit-Risk Analysis.
- Can accommodate both objective harms and subjective benefits.
- Avoids the invalid assumption of a linear relationship between severity and risk, as is present in methods or benefit-risk analysis that assign integers from 1 to 5 to the five categories of severity in Table 4 of TR 24971.
- Is significantly more objective than prior Benefit-Risk Analysis techniques, including guidelines suggested by FDA<sup>3</sup>.
- The steps used to simplify  $B > R$  are intuitively obvious, making acceptance of the analysis' conclusion easier than with less-intuitive analysis methods.
- The conclusion is normally intuitively obvious, making acceptance of the analysis' conclusion easier than with less-intuitive analysis methods.
- Can incorporate the preferences of individuals.
- Can account for the uncertainty around inputs to the analysis.
- Can account for the duration and timing of risks and benefits, including changes over time.
- Is neutral, reaching conclusions that a product's Benefits exceeds its Risks just as easily as the conclusion that a product's Risks exceeds its Benefits.

At the foundation, we have shown how to use 'risk' metrics to estimate the 'benefit' of a medical treatment. After establishing this novel use of risk metrics, Equation 9 is derived from the test "does the

benefit of a medical treating exceed the risk to the patient from the treatment?”, which is summarized in Equation 1 as  $B > R$ . The ‘risk algebra’ in Attachment A will simplify Equation 9 until it is intuitively obvious whether Equation 9 is true (i.e., whether benefit outweighs risk) or not.

## Attachment A- Risk Algebra

We will explain how to simplify Equation 9's tables of risks until Equation 1 is shown to be true or false.

### 'Risk Algebra' Concepts

Now that we've developed Equation 9, we need to develop a way to simplify Equation 9 until it is clear whether the benefit exceeds the risk, or the risk exceeds the benefit. Everyone reading this paper will be familiar with using algebra to simplify an equation with numbers until the answer is given. By analogy, we will determine whether Equation 9 is true by using 'risk algebra' to simplify Equation 9 until the answer is given. Building on this analogy with using algebra to solve equations with numbers, we will review the steps of solving an equation with numbers before generalizing that process to Equation 9.

If we want to solve the equation  $3x^2 + 7 = 55$  for the number,  $x$ , the steps are:

<b>Equation</b>	<b>Simplification Step</b>
$3x^2 + 7 = 55$	Original Equation – No simplification
$3x^2 + 7 - 7 = 55 - 7$	Subtract a number from both sides
$3x^2 + 0 = 48$	Simplify the Addition on both sides
$\frac{3x^2}{3} = \frac{48}{3}$	Divide by a number on both sides
$\frac{3}{3}x^2 = 16$	Simplify the Division on both sides
$\sqrt{x^2} = \sqrt{16}$	Take the square root of both sides
$x = 4$	The final answer – No simplification

In general, the 'trick' to simplifying an equation with numbers is this: As long as we simplify the equation by doing the same 'thing' to both sides of the equation, that 'thing' does not change the equation's equality. Since our simplification steps do not change the equation's equality, the answer for the final equation is the same answer as the answer for the first equation.

While readers who are familiar with abstract algebra can verify the technical correctness of the following statement, the rule that "we simplify the equation by doing the same 'thing' to both sides of the equation, that 'thing' does not change the equation's equality" is just as true for Equation 9 as it is for the real-number equation we just reviewed. In other words, as long as we simplify Equation 9 by adding, subtracting, or rearranging the same risk, in the same way, to both sides of Equation 9, we can ensure that, when we simplify Equation 9, we never change a false equation to a true one. This enables us to infer, if the simplified version of Equation 9 is true, that Equation 1 is true.

We will develop four ‘risk algebra’ rules for simplifying Equation 9:

- Two ‘rules’ simplify Equation 9 by removing risks:
  - Removing Identical Risks
  - Removing Unequal Risks
- Two ‘rules’ move Risks within in Equation 9 in preparation for the previous rules removing them:
  - Moving Repeated Risks
  - Moving Similar Risks

**An Example for Illustration**

While illustrating how to use ‘risk algebra’ to simplify Equation 9, we will start with the following ‘counts’ in the cells in Equation 9:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	4	1	3	0	0
Probable	4	3	4	0	1
Occasional	3	0	2	3	0
Remote	7	3	4	6	1
Improbable	5	5	1	3	0

 $\succsim$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	2	4	0	0	0
Probable	15	4	2	1	0
Occasional	4	10	2	1	1
Remote	4	5	4	3	1
Improbable	5	6	1	12	0

Equation 10

This example of counts was designed for illustrating how to use risk algebra and does not represent a true Benefit-Risk Analysis. In contrast, Attachments A and B each contain an example that uses this paper’s method to perform a Benefit-Risk Analysis for a medically realistic situation.

A cursory review of Equation 10 shows that the sum of all the numbers on the right-hand side of the equation greater than the sum of the numbers on the left-hand side; i.e., the right-hand side contains more risks than the left-hand side. Additionally, both tables contain the same number of catastrophic risks. These observations might lead to the conclusion that the risk after the medical treatment is higher than the risk before; i.e., the medical treatment’s risk exceeds its benefit.

The next sections of this paper will use ‘Risk Algebra’ to simplify Equation 10, with the goal of simplifying the tables sufficiently that it is intuitively clear whether benefit exceeds risk; i.e., whether the left-hand side of Equation 10 represents more risk than the right-hand side. Thus, the simplified equation will illustrate the importance of using risk algebra to simplify Equation 10 because the simplified tables will show that the medical treatment’s benefit does exceeds its risk (i.e., show that the tentative conclusion in the previous paragraph is incorrect).

**Removing Identical Risks**

If we find recognize that the same ordered pair,  $(P_i, S_i)$  appears on both sides of the inequality in Equation 9, then it makes sense that removing that ‘same’ ordered pair both sides of Equation 9 does not change which side of Equation 9 has the greater risk. That is, if  $b$  represents a single ordered pair of probability and severity, then  $\{a, b\} \succsim \{c, b\}$  implies the simpler equation  $\{a\} \succsim \{c\}$ .



In order to recognize that the same ordered pair,  $(P_i, S_i)$  appears on both sides of the inequality in Equation 9, we need to remember that the number that appears in each cell of Equation 9 represents the number of risks that share the probability and severity,  $(P_i, S_i)$ , of that row and column (respectively) of the matrix. Therefore, if we look for all of the instances in Equation 9 where the same cell has a non-zero number on both sides of the equation, then we will identify all of the instances where the same ordered pair appears on both sides of the inequality in Equation 9. And “removing one (or two or etc.) of these ordered pairs from this cell” means we subtract ‘1’ (or ‘2’, or etc.) from the same cell on both sides of Equation 9.

If you look at Equation 10, you can see that the cell at the junction of ‘Frequent’ and ‘Negligible’ has 4 risks on the left-hand side of Equation 10 and 2 risks on the right-hand side. By applying “Removing Identical Risks” to both sides of Equation 10, we can remove two Frequent/Negligible risks from each side of Equation 10 without changing whether the equation is true. Therefore, we will remove two Frequent/Negligible risks from both sides of Equation 10 by subtracting 2 from the Frequent/Negligible cell on each side of Equation 10, as is shown in Equation 11:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	4-2 = 2	1	3	0	0
Probable	4	3	4	0	1
Occasional	3	0	2	3	0
Remote	7	3	4	6	1
Improbable	5	5	1	3	0

 $\S$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	2-2 = 0	4	0	0	0
Probable	15	4	2	1	0
Occasional	4	10	2	1	1
Remote	4	5	4	3	1
Improbable	5	6	1	12	0

Equation 11

After the have been performed, the previous equation simplifies to:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	2	1	3	0	0
Probable	4	3	4	0	1
Occasional	3	0	2	3	0
Remote	7	3	4	6	1
Improbable	5	5	1	3	0

 $\S$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	4	0	0	0
Probable	15	4	2	1	0
Occasional	4	10	2	1	1
Remote	4	5	4	3	1
Improbable	5	6	1	12	0

Equation 12

By applying “Removing Identical Risks” to all of the possible places in Equation 12, we see the following subtractions to remove identical Risks:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Frequent	2	1-1 = 0	3	0	0
Probable	4-4 = 0	3-3 = 0	4-2 = 2	0	1
Occasional	3-3 = 0	0	2-2 = 0	3-1 = 2	0
Remote	7-4 = 3	3-3 = 0	4-4 = 0	6-3 = 3	1-1 = 0
Improbable	5-5 = 0	5-5 = 0	1-1 = 0	3-3 = 0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Frequent	0	4-1 = 3	0	0	0
Probable	15-4 = 11	4-3 = 1	2-2 = 0	1	0
Occasional	4-3 = 1	10	2-2 = 0	1-1 = 0	1
Remote	4-4 = 0	5-3 = 2	4-4 = 0	3-3 = 0	1-1 = 0
Improbable	5-5 = 0	6-5 = 1	1-1 = 0	12-3 = 9	0

Equation 13

After the subtractions in Equation 13 have been performed, Equation 13 simplifies to Equation 14:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	2	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	11	1	0	1	0
Occasional	1	10	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

Equation 14

Since  $R_B$  and  $R_A$  contain risks to the patient’s health before, and after, respectively, the medical treatment, and since  $R_B$  and  $R_A$  are on opposite sides of the inequality in Equation 9, **Removing Identical Risks** will eliminate all of the patient health risks that are not affected by the medical treatment. Therefore, depending on the depth of detail in the patient health model, the first application of **Removing Identical Risks** may eliminate a quite a few Risks on both sides of the inequality in Equation 9.

**Moving Repeated Risks**

Because the rows in Equation 9 represent probability, we can change which row holds the ‘count’ for a risk if we change the number of occurrences of the risk to maintain the same probability. In general, if a cell contains a count of  $n$  risks, then we can move some, or all, of the risks down one row by:

- a) In the original cell, reducing  $n$  by any positive integer less than or equal to  $n$ , say  $i$ . So, the ‘count’ in the original cell changes from  $n$  to  $n - i$ .
- b) Multiplying  $i$  by the factor used to decrease probability range from the original row to the row below,  $F_p$ , and
- c) Adding  $i \times F_p$  to the ‘count’ in the cell below the original cell.

For example,

- Since we are using Table 4 to define the probability in each row of Equation 9, then, in the left-hand side of Equation 14, the row below 'Frequent' (named 'Probable') has a probability range that is  $1/10^{\text{th}}$  the probability range of 'Frequent'; i.e.,  $F_p = 10$ .
- The Frequent / Negligible cell in the left-hand side of Equation 14 has a value of '2'; i.e.,  $n = 2$ .
- Reduce the count in the Frequent / Negligible cell in the left-hand side of Equation 14 by '1'; i.e.,  $i = 1$ .
- Increase the count in the Probable / Negligible cell in the left-hand side of Equation 14 by '10'; i.e.,  $i \times F_p$ .

The result of the previous four bullets is to change Equation 14 to:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	2 - 1 = 1	0	3	0	0
Probable	0 + 1 * 10 = 10	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	11	1	0	1	0
Occasional	1	10	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

Equation 15

We can now show that the reason for using the **Moving Repeated Risks** rule is that we can use the **Moving Repeated Risks** rule to simplify Equation 15, while we could not use **Moving Repeated Risks** on Equation 14.

Using **Moving Repeated Risks** on Equation 15 gives:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	10 - 10 = 0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	11 - 10 = 1	1	0	1	0
Occasional	1	10	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

or

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1	0	1	0
Occasional	1	10	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

Equation 16

There are many variants on **Moving Repeated Risks**; e.g., while the previous example moved a Risk 'count' *down* one row to increase the count of a risk, we can also move a Risk count *up* one row to reduce the count of risk, as is shown in the next example:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1+1=2	0	1	0
Occasional	1	10-10=0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

or

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9	0

Equation 17

Finally, we can also add identical risks to both sides of a risk equation without changing whether the equation is true in order to set-up other risk algebra rules; e.g., we can 'add' an 'Improbable / Critical' risk to both sides of Equation 17, as shown below:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	0+1=1	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	9+1=10	0

Adding this risk enables us to use **Moving Repeated Risks**, followed by **Removing Identical Risks** to simplify the previous equation as follows:

- First: Using **Moving Repeated Risks** on the previous equation, we get:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0+1 = 1	0
Improbable	0	1	0	10-10 = 0	0

- Second: Using **Removing Identical Risks** on the previous equation, we now get:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	3-1 = 2	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	1-1 = 0	0
Improbable	0	1	0	0	0

which reduces to

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1	0	3	0	0
Probable	0	0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_{AUR}$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

Equation 18

### Moving Similar Risks

The previous algebraic rule was built on the concept that we can represent the same risk in different cells of Table 6 by moving the 'count' for a risk to different rows within the same severity. This algebraic rule generalizes the concept of representing the same risk in different cells by moving the 'count' for a risk across a band of cells with similar risks. In the following table, combinations of Severity and Probability with the same number and color have approximately the same amount of risk:

		Qualitative <b>severity</b> levels				
		Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Semi-quantitative <b>probability</b> levels	Expected	7	8	9	10	11
	Often	6	7	8	9	10
	Frequent	5	6	7	8	9
	Probable	4	5	6	7	8
	Occasional	3	4	5	6	7
	Remote	2	3	4	5	6
	Improbable	1	2	3	4	5

Table 9 – Bands of Similar Risk

For example, a ‘Remote - Serious/Major’ risk is in a cell of Table 9 with a number ‘4’. This means we can move the ‘count’ for this risk to another cell within band number ‘4’, like ‘Occasional – Minor’ or ‘Improbable – Critical’.

- NOTE<sup>31</sup>:
- a) The first, and most important consideration to ensure **Moving Similar Risks** never changes a false equation to a true one is to construct risk metrics so changes in the level of probability and severity have roughly the same impact on patient risk. While the probability and severity tables in ISO/TR 24971 satisfy this assumption for most medical treatments, if you create your own severity and/or probability tables *and* if you want to use the ‘risk algebra’ of **Moving Similar Risks** to simplify Equation 9, then it is critical that the tables be constructed so this fundamental assumption is met; namely, that changes in the level of probability and severity have roughly the same impact on patient risk.
  - b) The second consideration is based on two core characteristics that matter when moving between severity categories:
    - Changes in severity category cause non-linear changes in patient risk, and
    - Severity changes increase monotonically from ‘Negligible’ to ‘Catastrophic/Fatal’.

Because of these two core characteristics, when using the ‘Move Similar Risks’ rule:

- 1) Avoid under-stating the risk by moving (like the above example) ‘Minor’ risks to ‘Catastrophic/Fatal’ risks. Instead, over-state the risk by moving risks from higher severities to lower severities without changing the number of risks. For example, moving *n* ‘Catastrophic/Fatal’ risks to *n* ‘Critical’ risks is conservative.

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<sup>31</sup> The fundamental problem with many risk metrics is that they assign sequential integers to each severity category; i.e., ‘1’ for ‘Negligible’ and ‘5’ for ‘Catastrophic/Fatal’. This leads to the conclusion that three ‘Minor’ harms as more important than one ‘Catastrophic/Fatal’ harm, which no one agrees with. A strength of this method is that the previous two rules of ‘Risk Algebra’ always work within the same severity level, so comparisons of the relative importance of three ‘Serious’ harms and one ‘Catastrophic/Fatal’ harm are avoided. However, the last two ‘risk algebra’ rules can word across severity levels, so we will take several steps to ensure these ‘risk algebra’ rules “never change a false equation to a true one”, as was stated in the section titled “Risk Algebra Concepts”.

Because the risk metrics can not be constructed so changes in the level of probability and severity have exactly the same impact on patient risk for all combinations of probability and severity,

- 2) Move as few risks as necessary to simplify the equation, but no more, and
- 3) Move the risks down as few severities as necessary to simplify the equation.

By applying the ‘risk algebra’ of **Moving Similar Risks** to Equation 18, we can note that we can move the Negligible/Frequent cell on the left-hand side of the equation, along the #5 ‘risk band’, to the Minor/Probable cell, as is done in the following equation:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	1-1=0	0	3	0	0
Probable	0	0+1=1	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

 $\Rightarrow$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

This change enables us to use **Removing Identical Risks** on the previous equation, as follows:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3	0	0
Probable	0	1-1=0	2	0	1
Occasional	0	0	0	2	0
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

 $\Rightarrow$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	2-1=1	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

Equation 19

Now we will combine all three of the ‘risk algebra’ rules to simplify the ‘Catastrophic/Fatal’ risks and then the ‘Critical’ Risks on both sides of Equation 19:

- First, we will use **Moving Repeated Risks** to the left-hand-side of Equation 19:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3	0	0
Probable	0	0	2	0	1-1=0
Occasional	0	0	0	2	0+10=10
Remote	3	0	0	2	0

 $\Rightarrow$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1	0	1	0
Occasional	1	0	0	0	1
Remote	0	2	0	0	0

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Improbable	0	0	0	1	0

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Improbable	0	1	0	0	0

- Second, we will use **Removing Identical Risks** on the 'Occasional – Catastrophic/Fatal' cells:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3	0	0
Probable	0	0	2	0	0
Occasional	0	0	0	2	10-1 = 9
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1	0	1	0
Occasional	1	0	0	0	1-1 = 0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

Note that this has eliminated all 'Catastrophic / Fatal' Risks from the right-hand side of the previous equation. Now we will eliminate all 'Critical' Risks from the right-hand side of the previous equation:

- First, we will use **Moving Similar Risks** to move the risks in the 'Catastrophic/Fatal' column of the left-hand side of the previous equation, along the #7 'risk band', to the 'Critical' Column:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3	0	0
Probable	0	0	2	0+1 = 1	0
Occasional	0	0	0	2	9-1=8
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1	0	1	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

- We can now use **Removing Identical Risks** to simplify both sides of the previous equation:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3	0	0
Probable	0	0	2	1-1 = 0	0
Occasional	0	0	0	2	8
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3	0	0	0
Probable	1	1	0	1-1 = 0	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

Equation 20

Note that this has eliminated all of the risks in the 'Critical' column of the right-hand side of the previous equation.



Previous simplifications have now eliminated all of the risks from the right-hand side of Equation 20 that are greater than 'Minor'. While it may now seem clear to some people that Equation 20 is true; i.e., the total risk on the left is greater than the total risk on the right, we will continue simplifying Equation 20 further to illustrate the fourth, and most powerful, 'risk algebra' rule, **Removing Unequal Risks**.

### Removing Unequal Risks

In the section titled **Removing Identical Risks**, we noted that  $\{a, b\} \succ \{c, b\}$  implies the simpler equation  $\{a\} \succ \{c\}$ . We will now do the same with unequal risks. The result will be very similar to **Removing Identical Risks**, but with one additional consideration.

Theory:

Consider our starting equation:  $\{a, b\} \succ \{c, d\}$ . We will introduce the symbology of  $|\{x\}|$  as a metric that measures the amount of risk in the set  $\{x\}$ . Since  $\{b\}$  is a set of risks that was removed from  $\{a\}$ , then  $\{a\} \cap \{b\} = \emptyset$ . But, because  $\{a\} \cap \{b\} = \emptyset$ , then  $|\{a, b\}| = |\{a\}| + |\{b\}|$ . Similarly,  $|\{c, d\}| = |\{c\}| + |\{d\}|$ . Therefore,  $\{a, b\} \succ \{c, d\}$  is equivalent to  $|\{a\}| + |\{b\}| \succ |\{c\}| + |\{d\}|$ . Since  $|\{a\}|$  is a lot of symbols, we will simplify the symbology so that  $a, b, c$ , and  $d$  represent the amount of risk in each set of risks and simplify  $\{a, b\} \succ \{c, d\}$  to  $a + b \succ c + d$ . With this symbology, we want to simplify  $a + b \succ c + d$  to  $a \succ c$ .

Since we are removing unequal risks, then either  $b \succ d$  or  $d \succ b$ , and we will consider each case in turn.

For the case where  $b \succ d$ :

If we start with Equation 9 written as  $a \succ c$ , and remove  $b_1$  from  $a$  (so,  $a_1 = a \ominus b_1$ ) and remove  $d_1$  from  $c$  (so,  $c_1 = c \ominus d_1$ ), then  $a_1 + b_1 \succ c_1 + d_1$  and  $b_1 \succ d_1$  implies that  $a_1 + (b_1 \ominus d_1) \succ c_1$ , where  $b_1 \ominus d_1 \succ 0$ .

Therefore, when we simplify  $a_1 + b_1 > c_1 + d_1$  to  $a_1 > c_1$ , the amount of risk on the left-hand side of the equation is reduced by the amount of  $b_1 \ominus d_1$ .

If we repeat the previous paragraph  $n$  times, then  $a \succ c$  becomes

$$a_n + \sum_{i=1}^n (b_i \ominus d_i) \succ c_n$$

and, simplifying the previous equation to  $a_n \succ c_n$ , then the amount of risk on the left-hand side of the equation is reduced by  $\sum_{i=1}^n (b_i \ominus d_i)$ .

As  $n$  increases, one of two things will happen first. Either:

1.  $c_n = 0$ ; i.e., there are more risks to remove on the left-hand side of the equation, but no more risks to remove from the right-hand side of the equation, or
2.  $a_n = 0$ ; i.e., there are more risks to remove on the right-hand side of the equation, but no more risks to remove from the left-hand side of the equation.

If the first case occurs, then we've shown that Equation 9 is true.

On the other hand, if the second case occurs, we haven't necessarily shown that Equation 9 is false. It is also possible that  $\sum_{i=1}^n (b_i \ominus d_i)$  grew larger than  $a_i \ominus c_i$ . The only way to tell which of these options occurred is to reverse the inequality in Equation 9 and simplify it again. Since, in this new equation,  $d \succ b$ , so

$$a_n \succ c_n + \sum_{i=1}^n (d_i \ominus b_i)$$

and the result of the simplification will be different than it was the first time.

For the case where  $d \succ b$ :

If we start with Equation 9 written as  $a \succ c$ , and remove  $b_1$  from  $a$  (so,  $a_1 = a \ominus b_1$ ) and remove  $d_1$  from  $c$  (so,  $c_1 = c \ominus d_1$ ), then  $a_1 + b_1 \succ c_1 + d_1$  and  $b_1 \succ d_1$  implies that  $a_1 \succ c_1 + (d_1 \ominus b_1)$ , where  $d_1 \ominus b_1 \succ 0$ .

Therefore, when we simplify  $a_1 + b_1 > c_1 + d_1$  to  $a_1 > c_1$ , the amount of risk on the right-hand side of the equation is reduced by the amount of  $d_1 \ominus b_1$ .

If we repeat the previous paragraph  $n$  times, then  $a \succ c$  becomes

$$a_n \succ c_n + \sum_{i=1}^n (d_i \ominus b_i)$$

and, simplifying the previous equation to  $a_n \succ c_n$ , then the amount of risk on the right-hand side of the equation is reduced by  $\sum_{i=1}^n (d_i \ominus b_i)$ .

As  $n$  increases, one of two things will happen first. Either:

1.  $c_n = 0$ ; i.e., there are more risks to remove on the left-hand side of the equation, but no more risks to remove from the right-hand side of the equation, or
2.  $a_n = 0$ ; i.e., there are more risks to remove on the right-hand side of the equation, but no more risks to remove from the left-hand side of the equation.

If the first case occurs, we haven't necessarily shown that Equation 9 is false. It is also possible that  $\sum_{i=1}^n (b_i \ominus d_i)$  grew larger than  $c_i$ .

And, if the second case occurs, we still haven't necessarily shown that Equation 9 is false. It is also possible that  $\sum_{i=1}^n (d_i \ominus b_i)$  grew larger than  $a_i \ominus c_i$ .

Comparing the two previous cases, we can see that the only option that enables us to conclude whether Equation 9 is true is the case where  $b \succ d$ . Therefore, we will only simplify Equation 9 by removing unequal risks if  $b \succ d$  is true.

Practice:

If  $\{b\}$  represents one or more risks,  $\{d\}$  represents one or more risks, and  $\{b\} \succ \{d\}$ , then  $\{a, b\} \succ \{c, d\}$  implies the simpler equation  $\{a\} \succ \{c\}$ .

NOTE<sup>31</sup>: When **Removing Unequal Risks**, if the simplified version of Equation 9 is true, then the original Equation 9 is also true. However, if  $\sum_{i=1}^n (\{b_i\} \hat{=} \{d_i\})$  becomes too large, it is possible to incorrectly show that Equation 9 is false. In order to minimize the chance this occurs, make each  $\{b_i\} \hat{=} \{d_i\}$  as small as possible. To pick the most extreme example possible: Do not use an ‘expected / catastrophic’ risk to remove a ‘improbable / negligible’ risk. Instead, pick risks for  $\{b\}$  that are as close to, and only slightly greater, than the risks for  $\{d\}$  as possible; e.g., to pick the best possible examples, use  $\{b\} = \{(occasional, critical)\}$  to remove  $\{d\} = \{(remote, critical)\}$ , or use  $\{b\} = \{(frequent, minor)\}$  to remove  $\{b\} = \{(occasional, minor)\}$ .

Looking at Equation 20, you may note there are 3 ‘Frequent-Serious/Major’ risks on the left-hand side and 3 “Frequent-Minor” risks on the right-hand side. Since the probabilities are the same and each ‘Serious/Major’ risk is larger than each ‘Minor’ risk, and since the larger risks are on the left-hand side of Equation 20, then the conditions for **Removing Unequal Risks** are met and we can simplify Equation 20 as follows:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	3-3 = 0	0	0
Probable	0	0	2	0	0
Occasional	0	0	0	2	8
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

 $\hat{=}$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	3-3 = 0	0	0	0
Probable	1	1	0	0	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

Looking at the previous equation, you may note there are 2 ‘Probable-Serious/Major’ risks on the left-hand side and 1 “Probable-Minor” risk and 1 ‘Probable-Negligible’ risk on the right-hand side. Since the probabilities are the same and a ‘Serious/Major’ risk is larger than either a ‘Minor’ risk or a ‘Negligible’ risk, and since the larger risks are on the left-hand side of Equation 20, then the conditions for **Removing Unequal Risks** are met and we can simplify Equation 20 as follows:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	2-1-1 = 0	0	0
Occasional	0	0	0	2	8
Remote	3	0	0	2	0
Improbable	0	0	0	1	0

 $\hat{=}$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	1-1 = 0	1-1 = 0	0	0	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

We can now use **Moving Similar Risks** and **Moving Repeated Risks** to position risks for the final simplification:

- First, we will use 'Move Similar Risks' to move the risks in the 'Remote-Critical' cell of the left-hand side of the previous equation, along the #5 'risk band', to the 'Probable-Minor' Cell:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0+1 = 1	0	0	0
Occasional	0	0	0	2	8
Remote	3	0	0	2-1 = 1	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

- Second, we will use **Moving Repeated Risks** to move the 'Probable-Minor' Risk down one row:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	1-1 = 0	0	0	0
Occasional	0	0+10 = 10	0	2	8
Remote	3	0	0	1	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	0	0	0	0
Remote	0	2	0	0	0
Improbable	0	1	0	0	0

- Finally, because the 10 'Occasional-Minor' risks on the left-hand side of the previous equation are each larger than the one 'Occasional-Negligible', the two 'Remote-Minor', and the one 'Improbable-Minor' Risks on the right-hand side of the previous equation, then all of the conditions are met to **Removing Unequal Risks** and we can simplify the previous equation as follows:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	10-1-2-1 = 6	0	2	8
Remote	3	0	0	1	0
Improbable	0	0	0	1	0

 $\approx$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1-1 = 0	0	0	0	0
Remote	0	2-2 = 0	0	0	0
Improbable	0	1-1 = 0	0	0	0

- Which simplifies to:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	6	0	2	8
Remote	3	0	0	1	0
Improbable	0	0	0	1	0

 $\Rightarrow$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

Equation 21

Since the right-hand side of Equation 21 has no risks and the left-hand side of Equation 21 has 21 risks, Equation 21 is clearly true. Since the ‘risk algebra’ simplifications will not change whether the original equation, Equation 10, is true or false does not change, then the fact that Equation 21 is true means that the original equation, Equation 10, is also true. We have, therefore, used ‘risk algebra’ to simplify Equation 10 until we can tell with certainty that it is true.

**Review and Document Equation 9 and its Simplification**

The creating and simplification of Equation 9 should be critically reviewed by a cross-functional team and the review documented. If the team is not comfortable with a step, they should not approve it. There are many ways to create and simplify Equation 9, so the team should change whatever they are not comfortable with to something more conservative and document why this more-conservative simplification was chosen.

This review should include:

- 1) Defining and/or deciding which health condition and treatment risks are included<sup>32</sup> and why,
- 2) Evaluating each pair of  $P_i^x$  and  $S_i^x$  values in Equation 9 and documenting why the probability and severity level was chosen,
- 3) Reviewing each simplification and documenting ‘why’ the team is comfortable with each simplification. The following sections highlight some possible areas of discussion by the cross-functional team that could be included in the Benefit-Risk analysis documentation.

a. **Removing Identical Risks**

This is the most straight-forward operation in ‘Risk Algebra’ and the documentation of applications of this rule should be similarly simple; e.g., simply listing each pair of identical ordered pairs,  $(P_i^x, S_i^x)$ , that are removed from each side of Equation 9.

b. **Moving Repeated Risks**

This operation has several options within it, so the documentation should include an explanation of which variation on ‘Moving Repeated Risks’ was followed and which ordered pairs,  $(P_i^x, S_i^x)$ , were effected.

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<sup>32</sup> The decision on which health condition and treatment risks to include impacts the scope of a Benefit-Risk Analysis; e.g., in a fully expanded version of Equation 9, as described in the application titled ‘Models of patient health’.)

- c. **Moving Similar Risks**  
There are two notes in the section **Moving Similar Risks** on how to ensure this 'risk algebra' rule is used properly. The documentation should include an explanation of the steps used to ensure these notes were implemented.
  - d. **Removing Unequal Risks**  
There a note in the section **Removing Unequal Risks** on how to ensure this 'risk algebra' rule is used properly. The documentation should include an explanation of the steps used to ensure this note was implemented.
- 4) If simplified version of Equation 9 says it is true, then it is true. However, if the simplified version of Equation 9 is false, then before concluding Equation 9 is false, try reversing the inequality in Equation 9 and simplifying the new equation. If the simplified version of this new equation is true, then you know Equation 9 is false.  
However, it is also possible that the simplified version of this new equation will be false again. This would indicate that Equation 9 is roughly equal and the following three steps should be taken, in order, to determine whether Equation 9 is true:
- a. There are many ways to create and simplify Equation 9, so review the process of populating Equation 9 for any opportunities to improve how the benefits and risks are represented, and, when simplifying Equation 9, try different sequences that might better maintain the amount of inequality between each side of Equation 9.
  - b. There will be instances where Equation 9 is so close to an equality that none of these techniques will be able to resolve for certain whether Equation 9 is true or not. In this case, the cross-functional team will need to select when the process of simplifying Equation 9 will stop. This same group will then need to either:
    - i. Use their intuition to interpret whether the simplified Equation 9 (or the simplified Equation 9 with the inequality reversed) is true or not, or
    - ii. Decide that Equation 9 is sufficiently close to an equality that the Equation 9 is false.

These steps would be captured in the Benefit-Risk Analysis documentation.

## Attachment B – Practical Examples of Benefit / Risk Analysis

### Overview

This attachment contains two examples of this paper's method to determine whether a medical procedure's benefit exceeds its risk:

- In the first example, the paper's method shows that the procedure's benefit exceeds the risk for a patient population.
- In the second example, the paper's method shows that the same procedure's risk exceeds the benefit for a different patient population.

In addition to demonstrating the method's equal ability to determine both that 'benefit exceeds risk' and that 'risk exceeds benefit', these examples also highlight the importance of the patient population to the result of a Benefit-Risk analysis.

### Application Steps

To determine whether a medical treatment's benefits exceed its risks:

Step 1) Define the medical treatment and patient population.

- a. Make sure the treatment options are broken down enough that there is only one Benefit-Risk decision being analyzed.
- b. Make sure the patient population is clear, as the risks vary significantly with the population.

Step 2) Identify the cross-functional team that will perform the Benefit-Risk analysis.

- a. The validity of the analysis is built on the depth and breadth of team members' expertise. Choose team members with the depth of knowledge necessary to understand the purpose and risks of applying the medical treatment to the patient population. Choose the variety of team members to cover all of the risks because no one person will have the depth of knowledge needed for all risks.

Step 3) Identify the risks in  $Table_{R_B}$ ,  $Table_{R_A}$ , and  $Table_R$ .

- a. This is the core of the method. Use the:
  - i. definitions of  $R_B$ ,  $R_A$ , and  $R$  (in footnotes 23, 24, and 25, respectively),
  - ii. team's chosen risk metric,
  - iii. team's expertise to identify the risks in  $R_B$ ,  $R_A$ , and  $R$ ,and populate the three tables with the identified risks.

Step 4) Use the tables for  $R_A$  and  $R$  to calculate  $R_A \cup R$ , and use  $R_B$  and  $R_A \cup R$  to populate Equation 9.

Step 5) Simplify Equation 9 until it is clear whether benefit exceeds risk.

- a. Use the 'risk algebra' described in Attachment A.

Step 6) Document the cross-functional team's concurrence with risks in  $Table_{RB}$ ,  $Table_{RA}$ , and  $Table_R$ , and the simplification of Equation 9.

- a. Capture the cross-functional team's rationale for supporting for each step of the process.

### Example #1

Step 1) Define the medical treatment and patient population

- a. Select the medical treatment and patient population on which you want to perform a Benefit-Risk analysis.
  - i. For this example, we will select a blood transfusion for the medical treatment and the patients in the United States who have sufficient upper GI bleeding to meet the ER's criteria for needing a transfusion for the patient population.

Step 2) Identify the members of the cross-functional team

- a. A physician who has worked in an 'emergency room' for over 10 years; i.e., a physician specialist who is expert in the practice of blood transfusions.
- b. A risk management engineer who has worked on apheresis equipment for over 10 years; i.e., an engineering specialist who is expert in the medical devices for collecting and infusing blood.

Normally, this list would include additional personnel (e.g., a representative from quality, production, post-market surveillance, etc., as the product's risk analysis needs dictate); however, because this example is being created to illustrate 'risk algebra' and not to make regulatory decisions, the cross-functional team is limited to these two people.

Step 3) Identify the risks in  $Table_{RB}$ ,  $Table_{RA}$ , and  $Table_R$

- a. For  $Table_{RB}$ :
  - i. Start generating  $Table_{RB}$  by identifying the health conditions that might cause this patient population to receive this medical treatment; i.e., for this example, the health conditions that might cause a bleeding ulcer to lose enough blood that a transfusion might be indicated to treat the blood loss.



<b>Medical Description of the Health Condition</b>	<b>Non-Specialist Description</b>
Altered Mental State	The patient becomes disoriented, more easily distracted, and less able to focus.
Circulatory Collapse	The patient has bled so much that the heart has too little blood volume to pump. Standard of care directs that such a patient has an endoscopy after the transfusion to identify / correct the reason for such extensive bleeding.
Heart attack, stroke, Kidney injury	The circulatory system cannot transport sufficient oxygen to sustain the body's organs.
Esophageal Varices	A pre-existing risk factor that can result in significant upper GI bleeding. Variceal bleeding accounts for 10–30% of all cases of upper gastrointestinal bleeding.

- ii. Identify the 'Health Condition' (from the previous table) as the 'Hazardous Situation' (as defined in ISO 14971, in the next table), identify one or more categories of severities of harm for each 'Health Condition' / Hazardous Situation, cite the reference used to determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ), and enter the category of probability for each severity of harm. Use Table 2 and Table 4 to assign probability and severity categories for the various scenarios associated with each Hazardous Situation.

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Altered Mental State	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Per Hemorrhagic shock: <a href="https://www.ncbi.nlm.nih.gov/books/NBK470382/">https://www.ncbi.nlm.nih.gov/books/NBK470382/</a> "Class 3: Volume loss from 30% to 40% of total blood volume, from 1500 mL to 2000 mL. A significant drop in blood pressure and changes in mental status occurs. Heart rate and respiratory rate are significantly elevated (more than 120 BPM). Urine output declines. Capillary refill is delayed."</li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-1}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-1}) \rightarrow P = Often</math></p>	Often	Expected	Often	Negligible
Circulatory Collapse	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Risk of circulatory collapse/altered mental status from GI bleeding - I would put this in the occasional category - difficult to fully assess. This imperfect study had &gt;50,000 patients but could only classify by the above means in a little over 5,000 of those patients.</li> </ul>	Expected	Expected	Expected	Minor

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
	<p>They had somewhere around 5% incidence of those patients that were class 3 or class 4, but the study population was ICU admissions which are already the sickest subset of all patients that have GI bleeding. Hence my reasoning to place this in the occasional category.</p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: and board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-0}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-0}) \rightarrow P = Expected</math></p>			Expected	Serious / Major
Heart attack, Stroke, Kidney injury	<p>For <math>P_1</math>: Probability: Per board-certified Emergency Room physician for over 10 years.</p>	Often	Often	Frequent	Catastrophic / Fatal
	<p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p>	Often	Expected	Often	Critical
	<p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-1}) \times (&lt; 10^{-1}) \rightarrow (&lt; 10^{-2}) \rightarrow P = Frequent</math>                      For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-1}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-1}) \rightarrow P = Often</math>                      For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-0}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-0}) \rightarrow P = Expected</math></p>	Expected	Expected	Expected	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Esophageal Varices	<p>For <math>P_1</math>: Per references from a board-certified Emergency Room physician for over 10 years:                      Between 1966 and 2013, there have been 50 cases of Esophageal Varices triggered by transfusions.                      Per the Red Cross, there are 29,000 transfusions per day, or 10,585,000 transfusions per year.                      Therefore, <math>50 / (47 \times 10,585,000) = 10^{-7} \rightarrow P_1 = \text{Improbable}</math></p> <p>For <math>P_2</math>: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-0}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-0}) \rightarrow P = \text{Expected}</math></p>	Expected	Expected	Expected	Catastrophic / Fatal

iii. Populate each cell in the following table for  $R_B$ :

- Note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R_B$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	1	2	0	1
Often	1	0	0	1	0
Frequent	0	0	0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

Table 10 -  $Table_{R_B}$  for the example in Attachment A

b. For  $Table_{R_A}$ :

- i. Generate  $Table_{R_A}$  by identifying the health conditions in this patient population that might remain after receiving the medical treatment.
  - 1. Since we are using  $B = R_B - R_A$ ,  $Table_{R_A}$  will normally contain the same health conditions as  $Table_{R_B}$  – particularly since  $Table_{R_B}$  contains any health risks that were created by the medical treatment.
  - 2. Per the board-certified Emergency Room physician for over 10 years for this example, the risks for  $R_A$  are the same as the risks for  $R_B$ .
  
- ii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more severities of harm for each ‘Health Condition’ / Hazardous Situation, and determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ). Use Table 2 and Table 4 to assign probability and severity levels for the various scenarios with each Hazardous Situation.

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Altered Mental State	For $P_1$ : Probability: <ul style="list-style-type: none"> <li>• Per Hemorrhagic shock: <a href="https://www.ncbi.nlm.nih.gov/books/NBK470382/">https://www.ncbi.nlm.nih.gov/books/NBK470382/</a> "Class 3: Volume loss from 30% to 40% of total blood volume, from 1500 mL to 2000 mL. A significant drop in blood pressure and changes in mental status occurs. Heart rate and respiratory rate are significantly elevated (more than 120 BPM). Urine output declines. Capillary refill is delayed."</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> For $P_2$ : Probability and Severity: Per board-certified Emergency Room physician for over 10 years. For $P (= P_1 \times P_2)$ : Probability: $(< 10^{-4}) \times (< 10^0) \rightarrow (< 10^{-4}) \rightarrow P = Occasional$	Expected	Expected	Expected	Negligible

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Circulatory Collapse	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Risk of circulatory collapse/altered mental status from GI bleeding - I would put this in the occasional category - difficult to fully assess. This imperfect study had &gt;50,000 patients but could only classify by the above means in a little over 5,000 of those patients. They had somewhere around 5% incidence of those patients that were class 3 or class 4, but the study population was ICU admissions which are already the sickest subset of all patients that have GI bleeding. Hence my reasoning to place this in the occasional category.</li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Book and board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-6}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Improbable	Expected	Improbable	<p>Minor</p> <hr/> <p>Serious / Major</p>
Heart attack, stroke, Kidney injury	<p>For <math>P_1</math>: Probability: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-6}) \times (&lt; 10^{-0}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Improbable	Expected	Improbable	Minor

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Esophageal Varices	<p>For <math>P_1</math>: Per references from the board-certified Emergency Room physician for over 10 years: Between 1966 and 2013, there have been 50 cases of Esophageal Varices triggered by transfusions. Per the Red Cross, there are 29,000 transfusions per day, or 10,585,000 transfusions per year. Therefore, <math>50 / (47 \times 10,585,000) = 10^{-7} \rightarrow P_1 = \text{Improbable}</math></p> <p>For <math>P_2</math>: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-6}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-6}) \rightarrow P = \text{Improbable}</math></p>	Improbable	Expected	Improbable	Catastrophic / Fatal

iii. Populate each cell in the following table for  $R_A$ .

- Note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R_A$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	2	1	0	1

Table 11 -  $Table_{R_A}$  for the example in Attachment A

c. Populate  $R$ :

- Identify the health conditions that, for this patient population, might remain after the blood transfusion.

Medical Description of the Health Condition	Non-Specialist Description
Febrile Nonhemolytic Reaction	Febrile non-hemolytic transfusion reaction (FNHTR) is the most common type of transfusion reaction. It is a benign occurrence with symptoms that include fever but not directly related with hemolysis. It is caused by cytokine release from leukocytes within the donor product as a consequence of white blood cell breakdown.
Allergic reaction to Tylenol or Benadryl	Typically, a rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.
Acute hemolytic transfusion reaction	An acute hemolytic transfusion reaction (AHTR) is triggered by host antibodies destroying donor red blood cells.
Graft vs. host disease	If the person receiving the transfusion has a compromised immune system.
TACO (Transfusion Associated Circulatory Overload)	Fluid overload, similar to acute congestive heart failure
Transfusion-related acute lung injury	Antibodies get activated, causing breathing issues
Infection	Patient acquires an infection from the needle or donated blood
Hepatitis B	Patient acquires Hepatitis B from the donated blood
Hepatitis A	Patient acquires Hepatitis A from the donated blood
HIV	Patient acquires HIV from the donated blood
Mislabelled blood bag	The label on the blood bag is affixed to the wrong bag

- ii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more severities of harm for each ‘Health Condition’ / Hazardous Situation, and determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ). Use Table 2 and to assign probability and severity levels for the various scenarios with each Hazardous Situation.



Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Febrile Nonhemolytic Reaction	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Febrile nonhemolytic transfusion reactions (FNHTRs) are commonly encountered transfusion reactions with overall per unit rate of 1%–3%. <a href="https://www.sciencedirect.com/science/article/abs/pii/B9780128137260000611">https://www.sciencedirect.com/science/article/abs/pii/B9780128137260000611</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-1}) \times (&lt; 10^{-2}) \rightarrow (&lt; 10^{-3}) \rightarrow P = Probable</math></p>	Often	Frequent	Probable	Minor
Allergic reaction to Tylenol or Benadryl (Successor Event to Febrile Nonhemolytic Reaction)	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Tylenol or Benadryl is administered after the patient receives a transfusion for Febrile Nonhemolytic Reaction. Reactions (to Tylenol) occur in 1.6% of all patients taking NSAIDs. <a href="https://www1.racgp.org.au/ajgp/2019/april/paracetamol-allergy-in-clinical-practice">https://www1.racgp.org.au/ajgp/2019/april/paracetamol-allergy-in-clinical-practice</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-0}) \times (&lt; 10^{-3}) \times (&lt; 10^{-1}) \rightarrow (&lt; 10^{-4}) \rightarrow P = Occasional</math></p>	Expected / (Probable, successor from previous row)	Often	Occasional	Serious / Major
Acute hemolytic	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>5 per 100,000</li> </ul>	Occasional	Occasional	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
transfusion reaction	<p><a href="https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-transfusion-reaction">https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-transfusion-reaction</a></p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-3}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Often	Occasional	Improbable	Critical
Graft vs. host disease	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>difficult to nail down incidence due to rarity of occurrence - some underlying risk factors are identified including prior bone marrow transplant</li> <li>Systematic review of Graft vs host disease in transfusion - <a href="https://ashpublications.org/blood/article/126/3/406/34566/A-systematic-review-of-transfusion-associated#">https://ashpublications.org/blood/article/126/3/406/34566/A-systematic-review-of-transfusion-associated#</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-6}) \times (&lt; 10^{-0}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Improbable	Expected	Improbable	Catastrophic / Fatal
TACO (Transfusion Associated)	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>TACO diagnosis recorded (17.1 per 100,000) <a href="https://www.fda.gov/science-research/fda-science-forum/outpatient-transfusions-and-occurrence-">https://www.fda.gov/science-research/fda-science-forum/outpatient-transfusions-and-occurrence-</a></li> </ul>	Occasional	Occasional	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Circulatory Overload)	<p>transfusion-associated-circulatory-overload-taco-among-us#:~:text=Results%3A,24.7%20for%20%E2%89%A55%20units.</p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math></p>		Occasional	Improbable	Critical
			Probable	Improbable	Catastrophic / Fatal
Transfusion-related acute lung injury	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Estimates of the incidence of TRALI have been 1 in 5,000 components, mostly in whole blood, 1 in 7,900 units of fresh frozen plasma, and 1 in 432 units of whole blood-derived platelet concentrates. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767181/#:~:text=TRALI%20has%20been%20reported%20following,derived%20platelet%20concentrates%20(13).">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767181/#:~:text=TRALI%20has%20been%20reported%20following,derived%20platelet%20concentrates%20(13)</a>.</li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math></p>	Frequent	Frequent	Occasional	Serious / Major
			Occasional	Improbable	Critical

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Infection	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>• 1/30,000 – Any Bacterial Infection.</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-2}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Occasional	Frequent	Improbable	Serious / Major
Infection	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>• 1/500,000 – Bacteremia Infection (Subsequent to bacterial infection)</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-0}) \rightarrow (&lt; 10^{-5}) \rightarrow P = \textit{Remote}</math></p>	Remote	Expected	Remote	Critical
Hepatitis B	<p>For <math>P</math>: Hepatitis B virus: 1:1 million to 1:1.5 million incidences of Hepatitis B being acquired from a blood transfusion.  <a href="https://www.uptodate.com/contents/image?imageKey=HEME%2F69661">https://www.uptodate.com/contents/image?imageKey=HEME%2F69661</a></p>	N/A	N/A	Improbable	Critical
Hepatitis C	<p>For <math>P</math>: Hepatitis C virus: 1:2 million to 1:2.6 million incidences of Hepatitis C being acquired from a blood transfusion.  <a href="https://www.uptodate.com/contents/image?imageKey=HEME%2F69661">https://www.uptodate.com/contents/image?imageKey=HEME%2F69661</a></p>	N/A	N/A	Improbable	Critical

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
HIV	For $P$ : The odds of acquiring HIV from a blood transfusion is less than 1 in two million. <a href="https://hhma.org/healthadvisor/aha-hivtrans-crs/#:~:text=What%20are%20the%20chances%20of,1%20in%20nearly%202%20million.">https://hhma.org/healthadvisor/aha-hivtrans-crs/#:~:text=What%20are%20the%20chances%20of,1%20in%20nearly%202%20million.</a>	N/A	N/A	Improbable	Critical
Mislabeled blood bag	For $P$ : actual harmful events due to errors occurred in 0.26% of the patients. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782493/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782493/</a>	N/A	N/A	Often	Negligible
				Frequent	Serious / Major
				Probable	Catastrophic / Fatal

iii. Populate each cell in the following table for  $R$ .

- Note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	0	3	6	3

Table 12 - Table<sub>R</sub> for the example in Attachment A

Step 4) Use the tables to calculate  $R_A \cup R$  and populate Equation 9

- Use  $R_A$  and  $R$ , Table 11 and Table 12 above, to calculate  $R_A \cup R$ :

$R_A$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	2	1	0	1

 $\cup$ 

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	0	3	6	3

 $=$ 

$R_A \cup R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

Equation 22

b. Use  $R_B$  (per Table 6 and footnote 23) and  $R_A \cup R$  (per the result of Equation 22) to populate Equation 9:

$R_B$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	1	2	0	1
Often	1	0	0	1	0
Frequent	0	0	0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\setminus$ 

$R_A \cup R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

Equation 23

Step 5) Simplify Equation 9 until it is clear whether benefit exceeds risk

a. Use “Removing Identical Risks” to simplify Equation 23:

If you look at Equation 23, you can see that the cell at the junction of ‘Often’ and ‘Negligible’ has 1 risk on the left-hand side of Equation 23 and 1 risk on the right-hand side. By applying “Removing Identical Risks” to both sides of Equation 23, we can remove one Often/Negligible risk from each side of Equation 23 without changing which side of the equation has the most risk. Therefore, we will remove the Often/Negligible risk from both sides of Equation 23 by subtracting 1 from the Often/Negligible cell on each side of Equation 23, as is shown in Equation 24:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	1	2	0	1
Often	(1-1=0)	0	0	1	0
Frequent	0	0	0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	(1-1=0)	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

Equation 24

Careful examination of Equation 24 shows there are no additional opportunities to simplify the equation with the “Removing Identical Risks” rule of ‘Risk Algebra’.

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	1	2	0	1
Often	0	0	0	1	0
Frequent	0	0	0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

Equation 25

b. Use the “Moving Redundant Risks” and “Removing Identical Risks” rules of ‘Risk Algebra’ to position Risks for further simplification:

If you look at Equation 25, you can see that:

- i. On the left-hand side, there is an ‘Expected / Minor’ risk.
- ii. On the right-hand side, there are an ‘Expected / Negligible’ and a ‘Frequent / Serious /Major’ risk.
- iii. If we use ‘Moving Redundant Risks’ on the left-hand side’s ‘Expected / Minor’ risk, we can get 10 ‘Often / Minor’ risks without changing which side of the equation has the most risk.

This puts 10 ‘Often / Minor’ risks on the left-hand side of the equation between the ‘Expected / Negligible’ and a ‘Frequent / Serious / Major’ risks on the right-hand side of the equation.

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	1 → 0 + 10	2	0	1
Often	0	0 + 10	0	1	0
Frequent	0	0	0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_A U R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

iv. We can then use ‘Moving Similar Risks’ to move one risk from the left-hand side’s ‘Often / Minor’ to the ‘Expected / Negligible’ and move another risk to the ‘Frequent / Serious / Major’ risk without changing which side of the equation has the most risk.

At this point, Equation 25 has become:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0 + 1 = 1	0	2	0	1
Often	0	10 - 2 = 8	0	1	0
Frequent	0	0	0 + 1 = 1	0	1

$R_A U R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	1	0	0



$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

v. If you look at the previous equation, you can see there is an ‘Expected / Negligible’ and a ‘Frequent / Serious / Major’ risk on both the left-hand and right-hand side of the equation. Therefore, by applying “Removing Identical Risks” to both sides of Equation 23, we can remove an ‘Expected / Negligible’ risk and a ‘Frequent / Serious / Major’ risk from each side of the equation without changing which side of the equation has the most risk. The result is:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1 - 1 = 0	0	2	0	1
Often	0	8	0	1	0
Frequent	0	0	1 - 1 = 0	0	1
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	1 - 1 = 0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	1 - 1 = 0	0	0
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

Equation 26

c. Equation 26 now has a pattern that is useful for simplifying the remainder of the equation. Both sides of the equation have no risks in the ‘Negligible’ column. For all of the other columns, the left-hand side has at least one risk in each column and in the three most-frequent rows, and the right-hand side has much larger numbers of risks in each column and in the least-frequent four rows.

While we can continue simplifying **Error! Reference source not found.** further, some people will look at the just-described pattern in Equation 26 and say it is now intuitively obvious that the risk total in the left-hand side of Equation 26 is greater than the risk total in the right-hand side of Equation 26 and, therefore, the benefits of giving the patient population a transfusion exceeds the risk of giving the patient population a transfusion.

However, if someone disagreed that this conclusion was intuitively obvious, they could always continue the simplification process until they feel the conclusion is intuitively obvious.

- d. By use the “Moving Redundant Risks” on each column of the left-hand side of the equation, we will have enough risks on in each column of the left-hand side of the equation to cancel all of the risks in the same column on the right-hand side of the equation.
  - i. On the left-hand side of Equation 26, we will use “Move Repeated Risks” once for each of the three right-most columns. This gives us the equation:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	2 →1 + 10	0	1
Often	0	8	0 + 10	1 → 0 + 10	0
Frequent	0	0	0	0 + 10	1 → 0 + 10
Probable	0	0	0	0	0 + 10
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\sum$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	1	0	0	0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	4

- ii. If we use “Remove Unequal Risks” on the ‘Catastrophic / Fatal’ column of the previous equation, we will get:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	1	0	1
Often	0	8	10	0	0
Frequent	0	0	0	10	0
Probable	0	0	0	0	10 - 4 = 6
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	1	0	0	4 - 4 = 0
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	2	4	6	0

So, the left-most and right-most columns of the right-hand side of the equation now have no risks.

iii. If we use “Remove Unequal Risks” on the ‘Critical’ and ‘Serious / Major’ column of the previous equation, we will get:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	1	0	1
Often	0	5	10 - 6 = 4	0	0
Frequent	0	0	0	10 - 7 = 3	0
Probable	0	0	0	0	6
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\approx$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	2 - 2 = 0	0	0
Remote	0	0	0	1 - 1 = 0	0
Improbable	0	0	4 - 4 = 0	6 - 6 = 0	0

*Equation 27*

- e. Equation 27 now no risks left on the right-hand side of the equation and 19 risks left on the left-hand side of the equation. Therefore, Equation 27 has more risks on the left-hand side of the equation and the equation is true.

Since Equation 27 is true, and since we reached Equation 27 from Equation 23 using operations that won't change which side of the equation has more risk, then Equation 23 is also true. And because Equation 23 is, then we have shown that, for this patient population, the benefit of a blood transfusion outweighs the risk.

#### Step 6) Document the cross-functional team's concurrence

Once Equation 9 has been simplified, the cross-functional team should review the risks in  $Table_{R_B}$ ,  $Table_{R_A}$ , and  $Table_R$  for completeness and concurrence with the risk metrics. If this review causes changes, then the simplification process will need to be repeated. If this review does not result in any changes, then the team's thinking should be documented.

Similarly, the cross-functional team should review the steps taken to simplify Equation 9. Considerations for each risk algebra operation are listed at the end of the explanation of each explanation. The team should confirm they still agree with each simplification step. If this review causes changes, then the simplification process will need to be repeated. If this review does not result in any changes, then the team's thinking should be documented.

This documentation should be released as part of the Benefit-Risk Analysis document.

### Example #2

#### Step 1) Define the medical treatment and patient population

- a. Select the medical treatment and patient population on which you want to perform a Benefit-Risk analysis.
  - i. For this example, we chose a blood transfusion for the medical treatment and chose the patients in the United States who have upper GI bleeding for the patient population. These patients may, or may not, meet the ER's criteria for needing a transfusion.

#### Step 2) Identify the cross-functional team that will perform the Benefit-Risk analysis

- a. A physician who has worked in an ‘emergency room’ for over 10 years; i.e., a physician specialist who is expert in the practice of blood transfusions.
- b. A risk management engineer who has worked on apheresis equipment for over 10 years; i.e., an engineering specialist who is expert in the medical devices for collecting and infusing blood.

Normally, this list would include additional personnel (e.g., a representative from quality, production, post-market surveillance, etc., as the product’s risk analysis needs dictate); however, because this example is being created to illustrate ‘risk algebra’ and not to make regulatory decisions, the cross-functional team is limited to these two people.

Step 3) Identify the risks in  $Table_{RB}$ ,  $Table_{RA}$ , and  $Table_R$

a. For  $Table_{RB}$ :

- i. Start generating  $Table_{RB}$  by identifying the health conditions that might cause this patient population to receive this medical treatment; i.e., for this example, the health conditions that might cause a bleeding ulcer to lose enough blood that a transfusion might be indicated to treat the blood loss.

Medical Description of the Health Condition	Non-Specialist Description
Altered Mental State	The patient becomes disoriented, more easily distracted, and less able to focus.
Circulatory Collapse	The patient has bled so much that the heart has too little blood volume to pump. Standard of care directs that such a patient has an endoscopy after the transfusion to identify / correct the reason for such extensive bleeding.
Heart attack, stroke, Kidney injury	The circulatory system cannot transport sufficient oxygen to sustain the body’s organs.
Esophageal Varices	A pre-existing risk factor that can result in significant upper GI bleeding. Variceal bleeding accounts for 10–30% of all cases of upper gastrointestinal bleeding.

- ii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more categories of severities of harm for each ‘Health Condition’ / Hazardous Situation, cite the reference used to determine  $P$

(when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ), and enter the category of probability for each severity of harm. Use Table 2 and Table 4 to assign probability and severity categories for the various scenarios associated with each Hazardous Situation.

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Altered Mental State	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Per Hemorrhagic shock: <a href="https://www.ncbi.nlm.nih.gov/books/NBK470382/">https://www.ncbi.nlm.nih.gov/books/NBK470382/</a> "Class 3: Volume loss from 30% to 40% of total blood volume, from 1500 mL to 2000 mL. A significant drop in blood pressure and changes in mental status occurs. Heart rate and respiratory rate are significantly elevated (more than 120 BPM). Urine output declines. Capillary refill is delayed."</li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-4}) \rightarrow P = Occasional</math></p>	Occasional	Expected	Occasional	Negligible
Circulatory Collapse	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Risk of circulatory collapse/altered mental status from GI bleeding - I would put this in the occasional category - difficult to fully assess. This imperfect study had &gt;50,000 patients but could only classify by the above means in a little over 5,000 of those patients.</li> </ul>	Probable	Often	Occasional	Minor

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
	<p>They had somewhere around 5% incidence of those patients that were class 3 or class 4, but the study population was ICU admissions which are already the sickest subset of all patients that have GI bleeding. Hence my reasoning to place this in the occasional category.</p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: and board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-3}) \times (&lt; 10^{-1}) \rightarrow (&lt; 10^{-4}) \rightarrow P = Occasional</math></p>			Occasional	Serious / Major
Heart attack, Stroke, Kidney injury	<p>For <math>P_1</math>: Probability: Per board-certified Emergency Room physician for over 10 years.</p>	Often	Often	Improbable	Catastrophic / Fatal
	<p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p>	Often	Expected	Improbable	Critical
	<p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-1}) \rightarrow (&lt; 10^{-6}) \rightarrow P = Improbable</math>                      For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-2}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math>                      For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-2}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math></p>	Expected	Expected	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Esophageal Varices	<p>For <math>P_1</math>: Per references from the board-certified Emergency Room physician for over 10 years:                      Between 1966 and 2013, there have been 50 cases of Esophageal Varices triggered by transfusions.                      Per the Red Cross, there are 29,000 transfusions per day, or 10,585,000 transfusions per year.                      Therefore, <math>50 / (47 \times 10,585,000) = 10^{-7} \rightarrow P_1 = \text{Improbable}</math></p> <p>For <math>P_2</math>: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-7}) \times (&lt; 10^0) \rightarrow (&lt; 10^{-7}) \rightarrow P = \text{Improbable}</math></p>	Improbable	Expected	Improbable	Catastrophic / Fatal

iii. Populate each cell in the following table for  $R_B$ , note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R_B$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	1	1	0	0
Remote	0	0	0	0	0
Improbable	0	0	1	1	2

Table 13 -  $Table_{R_B}$  for the example in Attachment A

b. For  $Table_{R_A}$ :

i. Generate  $Table_{R_A}$  by identifying the health conditions in this patient population that might remain after receiving the medical treatment.



1. Since we are using  $B = R_B - R_A$ ,  $Table_{R_A}$  will normally contain the same health conditions as  $Table_{R_B}$  – particularly since  $Table_{R_B}$  contains any health risks that were created by the medical treatment.
  2. Per the board-certified Emergency Room physician for over 10 years for this example, the risks for  $R_A$  are the same as the risks for  $R_B$ .
- ii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more severities of harm for each ‘Health Condition’ / Hazardous Situation, and determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ). Use Table 2 and Table 4 to assign probability and severity levels for the various scenarios with each Hazardous Situation.

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Altered Mental State	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>• Per Hemorrhagic shock: <a href="https://www.ncbi.nlm.nih.gov/books/NBK470382/">https://www.ncbi.nlm.nih.gov/books/NBK470382/</a> "Class 3: Volume loss from 30% to 40% of total blood volume, from 1500 mL to 2000 mL. A significant drop in blood pressure and changes in mental status occurs. Heart rate and respiratory rate are significantly elevated (more than 120 BPM). Urine output declines. Capillary refill is delayed."</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-4}) \rightarrow (&lt; 10^{-9}) \rightarrow P = Improbable</math></p>	Remote	Occasional	Improbable	Negligible
Circulatory Collapse	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>• Risk of circulatory collapse/altered mental status from GI bleeding - I would put this in the occasional category - difficult to fully assess. This imperfect study had &gt;50,000 patients but could only classify by the above means in a little over 5,000 of those patients.</li> </ul>	Remote	Probable	Improbable	Minor

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
	<p>They had somewhere around 5% incidence of those patients that were class 3 or class 4, but the study population was ICU admissions which are already the sickest subset of all patients that have GI bleeding. Hence my reasoning to place this in the occasional category.</p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: and board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-5}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-8}) \rightarrow P = Occasional</math></p>			Improbable	Serious / Major
Heart attack, Stroke, Kidney injury	For $P_1$ : Probability: Per board-certified Emergency Room physician for over 10 years.	Improbable	Occasional	Improbable	Catastrophic / Fatal
	For $P_2$ : Probability and Severity: Per board-certified Emergency Room physician for over 10 years.	Often	Expected	Improbable	Critical
	For $P (= P_1 \times P_2)$ : Probability: $(< 10^{-6}) \times (< 10^{-4}) \rightarrow (< 10^{-10}) \rightarrow P = Improbable$	Expected	Expected	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Esophageal Varices	<p>For <math>P_1</math>: Per references from the board-certified Emergency Room physician for over 10 years:                      Between 1966 and 2013, there have been 50 cases of Esophageal Varices triggered by transfusions.                      Per the Red Cross, there are 29,000 transfusions per day, or 10,585,000 transfusions per year.                      Therefore, <math>50 / (47 \times 10,585,000) = 10^{-7} \rightarrow P_1 = \text{Improbable}</math></p> <p>For <math>P_2</math>: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-4}) \rightarrow (&lt; 10^{-8}) \rightarrow P = \text{Improbable}</math></p>	Occasional	Occasional	Improbable	Catastrophic / Fatal

iii. Populate each cell in the following table for  $R_A$ , note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R_A$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	1	1	2	1	2

Table 14 -  $Table_{R_A}$  for the example in Attachment A

- c. Populate  $R$ :
  - i. Identify the health conditions that, for this patient population, might remain after the blood transfusion.

<b>Medical Description of the Health Condition</b>	<b>Non-Specialist Description</b>
Febrile Nonhemolytic Reaction	Febrile non-hemolytic transfusion reaction (FNHTR) is the most common type of transfusion reaction. It is a benign occurrence with symptoms that include fever but not directly related with hemolysis. It is caused by cytokine release from leukocytes within the donor product as a consequence of white blood cell breakdown.
Allergic reaction to Tylenol or Benadryl	Typically, a rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.
Acute hemolytic transfusion reaction	An acute hemolytic transfusion reaction (AHTR) is triggered by host antibodies destroying donor red blood cells.
Graft vs. host disease	If the person receiving the transfusion has a compromised immune system.
TACO (Transfusion Associated Circulatory Overload)	Fluid overload, similar to acute congestive heart failure
Transfusion-related acute lung injury	Antibodies get activated, causing breathing issues
Infection	Patient acquires an infection from the needle or donated blood
Hepatitis B	Patient acquires Hepatitis B from the donated blood
Hepatitis A	Patient acquires Hepatitis A from the donated blood
HIV	Patient acquires HIV from the donated blood
Mislabelled blood bag	The label on the blood bag is affixed to the wrong bag

- ii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more severities of harm for each ‘Health Condition’ / Hazardous Situation, and determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ). Use Table 2 and Table 4 to assign probability and severity levels for the various scenarios with each Hazardous Situation.
  
- iii. Identify the ‘Health Condition’ (from the previous table) as the ‘Hazardous Situation’ (as defined in ISO 14971, in the next table), identify one or more severities of harm for each ‘Health Condition’ / Hazardous Situation, and determine  $P$  (when helpful, use  $P_1$  and  $P_2$  to determine  $P$ ). Use Table 2 and to assign probability and severity levels for the various scenarios with each Hazardous Situation.

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Febrile Nonhemolytic Reaction	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Febrile nonhemolytic transfusion reactions (FNHTRs) are commonly encountered transfusion reactions with overall per unit rate of 1%–3%. <a href="https://www.sciencedirect.com/science/article/abs/pii/B9780128137260000611">https://www.sciencedirect.com/science/article/abs/pii/B9780128137260000611</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-1}) \times (&lt; 10^{-2}) \rightarrow (&lt; 10^{-3}) \rightarrow P = Probable</math></p>	Often	Frequent	Probable	Minor
Allergic reaction to Tylenol or Benadryl (Successor Event to Febrile Nonhemolytic Reaction)	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Tylenol or Benadryl is administered after the patient receives a transfusion for Febrile Nonhemolytic Reaction. Reactions (to Tylenol) occur in 1.6% of all patients taking NSAIDs. <a href="https://www1.racgp.org.au/ajgp/2019/april/paracetamol-allergy-in-clinical-practice">https://www1.racgp.org.au/ajgp/2019/april/paracetamol-allergy-in-clinical-practice</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-0}) \times (&lt; 10^{-3}) \times (&lt; 10^{-1}) \rightarrow (&lt; 10^{-4}) \rightarrow P = Occasional</math></p>	Expected / (Probable, successor from previous row)	Often	Occasional	Serious / Major
Acute hemolytic	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>5 per 100,000</li> </ul>	Occasional	Occasional	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
transfusion reaction	<p><a href="https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-transfusion-reaction">https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-transfusion-reaction</a></p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-3}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Often	Occasional	Improbable	Critical
Graft vs. host disease	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>difficult to nail down incidence due to rarity of occurrence - some underlying risk factors are identified including prior bone marrow transplant Systematic review of Graft vs host disease in transfusion - <a href="https://ashpublications.org/blood/article/126/3/406/34566/A-systematic-review-of-transfusion-associated">https://ashpublications.org/blood/article/126/3/406/34566/A-systematic-review-of-transfusion-associated#</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-6}) \times (&lt; 10^{-0}) \rightarrow (&lt; 10^{-6}) \rightarrow P = \textit{Improbable}</math></p>	Improbable	Expected	Improbable	Catastrophic / Fatal
TACO (Transfusion Associated)	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>TACO diagnosis recorded (17.1 per 100,000) <a href="https://www.fda.gov/science-research/fda-science-forum/outpatient-transfusions-and-occurrence-">https://www.fda.gov/science-research/fda-science-forum/outpatient-transfusions-and-occurrence-</a></li> </ul>	Occasional	Occasional	Improbable	Serious / Major

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Circulatory Overload)	<p>transfusion-associated-circulatory-overload-taco-among-us#:~:text=Results%3A,24.7%20for%20%E2%89%A55%20units.</p> <ul style="list-style-type: none"> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math></p>		Occasional	Improbable	Critical
			Probable	Improbable	Catastrophic / Fatal
Transfusion-related acute lung injury	<p>For <math>P_1</math>: Probability:</p> <ul style="list-style-type: none"> <li>Estimates of the incidence of TRALI have been 1 in 5,000 components, mostly in whole blood, 1 in 7,900 units of fresh frozen plasma, and 1 in 432 units of whole blood-derived platelet concentrates. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767181/#:~:text=TRALI%20has%20been%20reported%20following,derived%20platelet%20concentrates%20(13).">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767181/#:~:text=TRALI%20has%20been%20reported%20following,derived%20platelet%20concentrates%20(13).</a></li> <li>Per board-certified Emergency Room physician for over 10 years.</li> </ul> <p>For <math>P_2</math>: Probability and Severity: Per board-certified Emergency Room physician for over 10 years.</p> <p>For <math>P (= P_1 \times P_2)</math>: Probability: <math>(&lt; 10^{-4}) \times (&lt; 10^{-3}) \rightarrow (&lt; 10^{-7}) \rightarrow P = Improbable</math></p>	Frequent	Frequent	Occasional	Serious / Major
			Occasional	Improbable	Critical

Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
Infection	For $P_1$ : Probability: <ul style="list-style-type: none"> <li>• 1/30,000 – Any Bacterial Infection.</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> For $P_2$ : Probability and Severity: Per board-certified Emergency Room physician for over 10 years. For $P (= P_1 \times P_2)$ : Probability: $(< 10^{-4}) \times (< 10^{-2}) \rightarrow (< 10^{-6}) \rightarrow P = \textit{Improbable}$	Occasional	Frequent	Improbable	Serious / Major
	For $P_1$ : Probability: <ul style="list-style-type: none"> <li>• 1/500,000 – Bacteremia Infection (Subsequent to bacterial infection)</li> <li>• Per board-certified Emergency Room physician for over 10 years.</li> </ul> For $P_2$ : Probability and Severity: Per board-certified Emergency Room physician for over 10 years. For $P (= P_1 \times P_2)$ : Probability: $(< 10^{-5}) \times (< 10^{-0}) \rightarrow (< 10^{-5}) \rightarrow P = \textit{Remote}$	Remote	Expected	Remote	Critical
Hepatitis B	For $P$ : Hepatitis B virus: 1:1 million to 1:1.5 million incidences of Hepatitis B being acquired from a blood transfusion. <a href="https://www.uptodate.com/contents/image?imageKey=HEME%2F69661">https://www.uptodate.com/contents/image?imageKey=HEME%2F69661</a>	N/A	N/A	Improbable	Critical
Hepatitis C	For $P$ : Hepatitis C virus: 1:2 million to 1:2.6 million incidences of Hepatitis C being acquired from a blood transfusion. <a href="https://www.uptodate.com/contents/image?imageKey=HEME%2F69661">https://www.uptodate.com/contents/image?imageKey=HEME%2F69661</a>	N/A	N/A	Improbable	Critical



Hazardous Situation	Reference Information	$P_1$	$P_2$	$P$	Severity
HIV	For $P$ : The odds of acquiring HIV from a blood transfusion is less than 1 in two million. <a href="https://hhma.org/healthadvisor/aha-hivtrans-crs/#:~:text=What%20are%20the%20chances%20of,1%20in%20nearly%202%20million.">https://hhma.org/healthadvisor/aha-hivtrans-crs/#:~:text=What%20are%20the%20chances%20of,1%20in%20nearly%202%20million.</a>	N/A	N/A	Improbable	Critical
Misabeled blood bag	For $P$ : actual harmful events due to errors occurred in 0.26% of the patients. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782493/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782493/</a>	N/A	N/A	Often	Negligible
				Frequent	Serious / Major
				Probable	Catastrophic / Fatal

iv. Populate each cell in the following table for  $R$ , note the severity (from the top row) and the probability (from the left column), and enter the number of risks in the previous table with that cell's combination of severity and probability:

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	0	3	6	3

Table 15 -  $Table_R$  for the example in Attachment A

Step 4) Use the tables to calculate  $R_A \cup R$  and populate Equation 9

a. Use  $R_A$  and  $R$ , Table 11 and Table 12 above, to calculate  $R_A \cup R$ :

$R_A$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	1	1	2	1	2

 $\cup$ 

$R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	0	0	3	6	3

 $=$ 

$R_A \cup R$	Negligible	Minor		Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0	0
Often	1	0	0	0	0	1
Frequent	0	0	1	0	0	0
Probable	0	1	0	0	1	0
Occasional	0	0	2	0	0	0
Remote	0	0	0	1	0	0
Improbable	1	1	5	7	5	5

Equation 28

b. Use  $R_B$  (per Table 6 and footnote 23) and  $R_A \cup R$  (the result of Equation 22) to populate Equation 9:

$R_B$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	1	1	0	0
Remote	0	0	0	0	0
Improbable	0	0	1	1	2

 $\cup$ 

$R_A \cup R$	Negligible	Minor	Serious / Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	2	0	0
Remote	0	0	0	1	0
Improbable	1	1	5	7	5

Equation 29

Step 5) Simplify Equation 9 until it is clear whether benefit exceeds risk

a. Use “Removing Identical Risks” to simplify Equation 23:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	1	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	1-1 = 0	1-1 = 0	2-2 = 0

}>

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1	0	0	1
Occasional	0	0	1	0	0
Remote	0	0	0	1	0
Improbable	1	1	5-1 = 4	7-1 = 6	5-2 = 3

a. Use "Move Redundant Risks":

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	1	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

}>

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	1-1 = 0+10	0	0	1
Occasional	0	0+10 = 10	1	0	0
Remote	0	0	0	1	0
Improbable	1	1	4	6	3

a. Use the #8 band to "Remove Identical Risks":

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1	1-1 = 0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\sqrt{\}$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	0	0	0	1
Occasional	0	10-1 = 9	1	0	0
Remote	0	0	0	1	0
Improbable	1	1	4	6	3

a. Using “Removing Unequal Risks” within the ‘Minor’, ‘Serious/Major’, ‘Critical’, and ‘Catastrophic/Fatal’ columns to simplify Equation 23:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	1-1 = 0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\sqrt{\}$ 

$R_AUR$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	0	0	0
Frequent	0	0	1	0	0
Probable	0	0	0	0	1
Occasional	0	9-1 = 8	1	0	0
Remote	0	0	0	1	0
Improbable	1	1	4	6	3

a. This simplifies to:

$R_B$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	0	0	0	0	0
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	0	0	0	0
Remote	0	0	0	0	0
Improbable	0	0	0	0	0

 $\supset$ 

$R_A \cup R$	Negligible	Minor	Serious /Major	Critical	Catastrophic / Fatal
Expected	0	0	0	0	0
Often	1	0	1	0	1
Frequent	0	0	0	0	0
Probable	0	0	0	0	0
Occasional	0	8	0	0	0
Remote	0	0	0	1	0
Improbable	1	1	4	6	3

It is intuitively obvious that the right-hand side of the previous equation has a greater total risk than the left-hand side, so Equation 10 is not true and the procedure’s risks outweigh its benefits.

Step 6) Document the cross-functional team’s concurrence

Once Equation 9 has been simplified, the cross-functional team should review the risks in  $Table_{R_B}$ ,  $Table_{R_A}$ , and  $Table_R$  for completeness and concurrence with the risk metrics. If this review causes changes, then the simplification process will need to be repeated. If this review does not result in any changes, then the team’s thinking should be documented.

Similarly, the cross-functional team should review the steps taken to simplify Equation 9. Considerations for each risk algebra operation are listed at the end of the explanation of each explanation. The team should confirm they still agree with each simplification step. If this review causes changes, then the simplification process will need to be repeated. If this review does not result in any changes, then the team’s thinking should be documented.

This documentation should be released as part of the Benefit-Risk Analysis document.

## Attachment C- Applications of the Method

### Operationalizing the Method

The implementation of this method can be best understood within the context of the evolution of risk management.

- In the 1990s, there were no comprehensive, generally-recognized methods for assessing product risk and the risks presented by medical devices, and the need for risk mitigations, were left to the professional discretion of the engineering team charged with developing the devices.
- In the 2000s, ISO 14971 provided a comprehensive approach to managing the risks presented by medical devices, including the need for risk mitigations. However, responsibility for performing this risk work largely remained with engineers.
- In the 2010s, the industry's risk maturity-level increased significantly. While the probability and severity events after ISO 14971's 'hazardous situation' were now generally estimated by medical personnel, engineers continued to complete the remainder of the Risk Management File.
- In the 2020s, risk maturity continued to grow. FMEAs were extended to include patient harms and the role of medical personnel expanded to include non-local effects.

Two trends emerge from the previous bullets:

1. Risk Management is becoming more formal and detailed over time, and
2. The work performed by medical personnel is increasing.

Because this method establishes the benefit of a medical treatment by looking at the change in the patient population's health concerns before and after a treatment, this method continues both identified trends. And just as these trends have required companies to make resource changes to support these changes, this method is a significant change from past practice and may require new resource changes.

With that said, the author wants to acknowledge that most companies hire physicians as the medical personnel and highlight alternative resources that the author has seen both significantly lighten the load on physicians and improve the quality of work.

- Sales and Marketing personnel very often have intimate knowledge of the literature and practices surrounding patients' health concerns and, while their contributions may need verification by medical personnel, these people may be able to characterize significant portions of the patients' health risks and dramatically reduce the work by medical personnel.
- Similarly, nursing staff who specialize in relevant health concerns can also the work and may be able to characterize significant portions of the patients' health risks.
- A third group who can lighten the load that is often given to physicians are clinicians and/or clinical researchers.

If addition to the people in the previous three bullets providing additional resources, it should be emphasized that Risk Management is an activity that is best performed cross-functionally<sup>33</sup>, so that the varied perspectives of a variety of people, are all fed into a common understanding of the risk. For this reason, determinations of the benefit of a treatment get stronger when the work of physicians are augmented by the people in the previous three bullets.

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<sup>33</sup> Cross-functional teams following ISO 14971 traditionally include members from Marketing/Sales, Medical Personnel, Engineering, Production, Complaint Investigation, etc.

### Using the Method for a PMA or 510(k)

Submissions to FDA to obtain 510(k) clearance to market a medical device are based on a company's ability to show equivalence of the product they want to market with a predicate device that was already on market in 1976 and whose efficacy (i.e., 'benefit') and safety (i.e., 'risk') have been shown over time to be acceptable. For this reason, a Benefit-Risk Analysis is not nearly as important for a 510(k) as for other submission to obtain clearance to market a device; e.g., a PMA (Pre-Market Authorization).

PMA submissions are for products that were introduced since 1976 and, for this reason, their efficacy and safety record is considered insufficient to gain approval to market based on the safety record of other PMA products. For PMA products, a Benefit-Risk Analysis is key to showing the product may be marketed.

Many products are based primarily on pre-1976 product technology but have added some new feature or medical treatment that did not exist prior to 1976. These products submission to FDA for clearance to market the product should be a blend of the methods in the two previous paragraphs:

For those features that are equivalent to pre-1976 products with an acceptable safety record, a 510(k) submission is appropriate.

For those features that were *not* present on any pre-1976 product with an acceptable safety record, a Benefit-Risk Analysis of these features is appropriate.

The submission for market clearance would, then, have elements of both 510(k) and PMA clearances to market a medical device.

### ISO 14971

ISO 14971 defines the concept of 'acceptable' and 'unacceptable' risks, based on a Risk Policy that is approved Top Management and establishes criteria for risk acceptability<sup>34</sup>. If this policy allows Risk Management decisions without considering acceptable risks, then the Benefit-Risk analysis in this method can be simplified to only unacceptable risks.

### Dominant Risks

While Equation 9 allows for a large number of risks to be considered, and while this can be necessary to show whether benefit exceeds risk for products when the amount of benefit and risk are nearly equal, Equation 9 can be quite simple if a few risks dominate the other Risks and the risk difference between the two sides of Equation 9 exceeds the size of those other Risks. In this case, Equation 9 can be simplified to only use a few, dominant Risks, although Equation 9 would still need to be accompanied by a justification for omitting the other Risks.

In at least one example, Equation 9 can have several large risks on the left-hand side of Equation 9,  $R_B$ , that the medical treatment reduces to small risks on the right-hand side of Equation 9 (e.g.,  $R_A$ , for the case of a highly effective medical therapy). In this case, it may immediately (or after a very few steps of 'risk algebra') be intuitively obvious that a few of the large risks on the left-hand side of Equation 9 are far bigger than all of the risks on the right-hand side of Equation 9,  $R_B \cup R$ .

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<sup>34</sup> Per the section of ISO 14971:2019+A11:2021 named 'Relationship between this European standard and the General Safety and Performance Requirements of Regulation (EU) 2017 /745 or 746 aimed to be covered', "The manufacturer's policy for determining acceptable risk must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 10, 11, 13, 15, 16, 17, 18 and 19 of the Regulation."

If this is the case, then the documentation of the Benefit-Risk analysis can use these dominant Risks to establish a maximum bound for all of the risks on the right-hand side of Equation 9 and reach the conclusion that 'benefit exceeds risk' by arguing that all of the risks on the right-hand side of Equation 9 are smaller than the maximum bound. (This can be formalized using 'risk algebra' by combining the removal of repeated Risks with the removal of unequal Risks.)

### Selecting the Best Therapy from a List of Alternative Therapies

In at least one example of the present disclosure, a method for selecting the best therapy from a list of alternative therapies is disclosed. Equation 4 has an interesting interpretation for selecting the best therapy from a list of alternative therapies:

$R^B$  can be interpreted as the patient's likely health outcome if nothing is done.

$R^A + R$  can be interpreted as the patient's likely health outcome if a therapy is performed.

Therefore, assuming Equation 9 is met for each alternative therapy, selecting the best therapy from a list of alternative therapies is equivalent to determining  $R^A + R$  for each therapy and then selecting the therapy with the minimum value for  $R^A + R$ .

### Adjusting the Weight given to Each Risk

#### Adapting to Individual Patient Preference

In at least one example of the present disclosure, a method to customize the Benefit-Risk Analysis to an individual patient is disclosed. We can use these weights to customize a Benefit-Risk Analysis to individual patients. Just as Benefit-Risk Analysis was shown, above, to facilitate selecting the best therapy from among alternative therapies, customizing a Benefit-Risk Analysis to an individual patient's preferences can be invaluable to facilitate holistic discussions with a patient about medical treatment options – ensuring that all factors are considered, and specific factors were not given excessive weight.

For example, a patient might prefer to maximize their quality of life during one or more upcoming life-events ((e.g., a birth or marriage) at the expense of quality of life after those life-events. Since the patient's preferences are time-based, we can multiply the 3-D plots of time-varying description of risks by a function that captures the patient's time-preferences. (The integration of the point-by-point product of two functions is a standard operation in calculus, referred to as a 'convolution integral'.)

For a simple case, if a patient cares only about their health for the next two years, the patient's time-preference is simply a 'box function' that is 1 unit high for the next two years and zero for all other times. Convoluting this 'box function' with the 3-D plot of each risk will provide a weight for each risk that is customized to the patient's preferences. Once the patient-specific weights are calculated, the weights for each cell in Tables 10 and 11 can be calculated and then simplified to determine whether the Benefit exceeds the Risk (for one therapy) or determine the best therapy (from a list of alternative therapies).

#### Accounting for Time-Varying Benefits and Risks

While, per section 3.18, ISO 14971 defines 'risk' as a combination of 'severity' and 'probability', FDA defines both risk and benefit a combination of 'severity', 'probability', and 'duration'<sup>3</sup>. This paper has previously provided a systematic framework for the first two of these factors: Severity and Probability. This section will expand that previous work to provide a systematic framework for all three factors: Severity, Probability, *and* Duration.



In at least one example of the present disclosure, a method to account for the effect of time on risk is disclosed. 'Time' is an important, and usually under-accounted for, factor of in risk management. While the duration of a risk is mentioned briefly in the 'Minor' level of severity in Table 4 of ISO / TR 24971 (documented in Table 2 of this paper), any accounting for time using ISO / TR 249971 becomes muddled because this same table also describe severities which are independent of time. In addition, some medical treatments require a significant amount of time before they produce benefits, and many such benefits may wear out and/or diminish over time. None of these factors are accounted for in Table 4 of ISO / TR 24971.

Turning now to Figure 4, we see a three-dimensional (3D) plot 100 of probability  $P$ , severity  $S$ , and time  $T$ . Specifically, probability  $P$  is shown on y-axis 102, severity  $S$  is shown on x-axis 104, and time  $T$  is shown on z-axis 106. Various risks  $R$  are shown (specifically,  $R_1$  108,  $R_2$  110,  $R_3$  112,  $R_4$  114, and  $R_5$  116, each of which are, as described above herein, combinations of a specific probability  $P$  and a severity  $S$ ). Thus,  $R_4$  114 is the combination of  $P_4$  118 and  $S_4$  120. To account for the changes in  $R_4$  over time,  $R_4$  can be extended along axis 106 to a point 122 at a time  $T_4$  124. The area 126 bounded by these axes therefore represents the weight based on time,  $W$ , given to a particular benefit or risk (in this example,  $R_4$ ) over time.

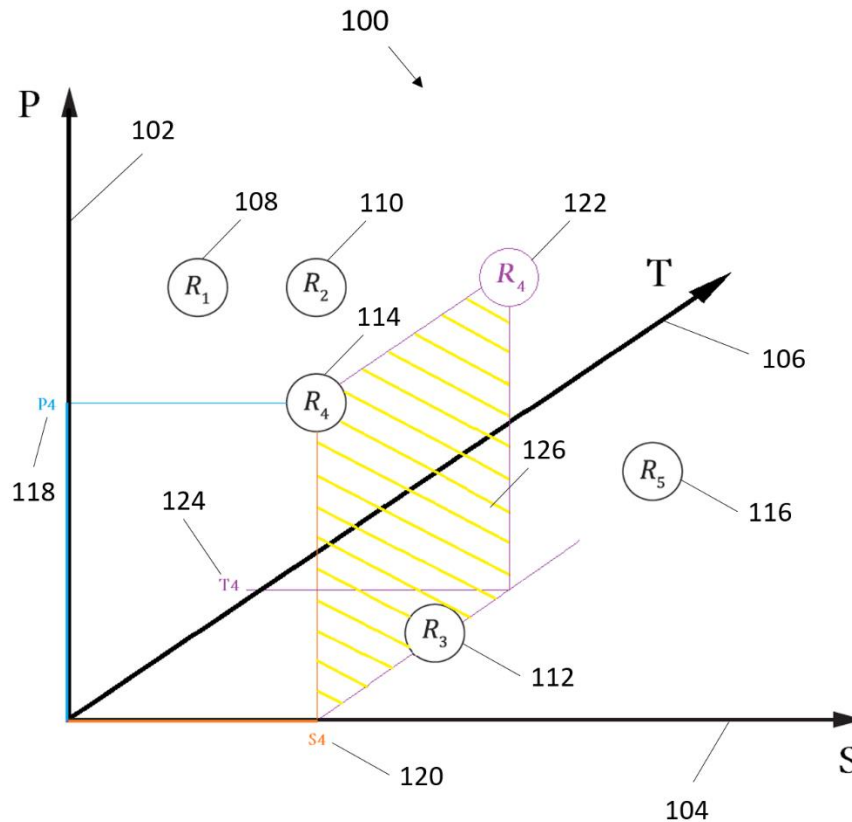


Figure 4 - Modeling the Effect of Time on Risk

We can generalize the area 126 to more complex shapes; e.g., where both the probability and severity are functions of time and the principles of integration, from calculus, are needed to determine the area (for two dimensions – time and either probability or severity) or volume (for three dimensions – probability, severity, and time). We will note that, since integration is available to handle arbitrarily complex changes over time, this paper will use only 2-dimensional, rectangular shapes in its examples.

While other embodiments are available, this paper will use area (or volume) as the weight for each risk to account for time; i.e., the  $i^{\text{th}}$  risk,  $R_i$ , is represented by the ordered triplet,

$$R_i = (P_i, S_i, W_i)$$

Equation 30

and the equation for  $R$  becomes:

$$R = \{(P_1, S_1, W_1), (P_2, S_2, W_2), (P_3, S_3, W_3), \dots, (P_n, S_n, W_n)\}$$

Equation 31

While there are different embodiments available for adding time-dependent weights to each risk, in an example addresses the case of modeling a benefit that does not begin until after a period of time has passed and then continues, unchanged, for the rest of the patient's life, we will define the following additional terms:

- $L$  is the patient's expected remaining lifetime,
- $T_i$  is the period of time before the benefit starts, and
- the model will linearly weight the benefit over time, based on how long the patient is expected to experience those benefits.

In this case, for the  $i^{\text{th}}$  risk,  $W_i = L - T_i$  and  $R_i = (P_i, S_i, L - T_i)$ .  $W_i$  can be modified to reflect the deferred value of the benefit not beginning immediately, but this modification may need to account for Patient Preference, as is described in the next section, titled "Adapting to Individual Patient Preference".

While, in general, each value of  $W_i$  will be calculated by a different equation, in the special case where every risk does not begin until after a period of time has passed, and Equation 31 becomes:

$$R = \{(P_1, S_1, L - T_1), (P_2, S_2, L - T_2), (P_3, S_3, L - T_3), \dots, (P_n, S_n, L - T_n)\}$$

To perform 'risk algebra' for risks with a weight that accounts for the variation of risk over time, first ensure that all of the risks have weights with the same dimension for time. Then, for each cell in Table 10, note the probability for that cell's row, the severity for that cell's column, add the weights for each risk in  $R_B$  with that same combination of probability and severity, and populated that cell with the sum of the weights for that combination probability and severity. Repeat this for Table 14, with the risks in  $R_A \cup R$ . (This is equivalent to what was described for risks without a weight for time if we assign  $W_i = 1$  for all values of  $i$ .)

The previously described 'risk algebra' rules works when risk is represented by a triplet (per Equation 30), as it did when risk was represented as an ordered pair (per Equation 3). The complication with Equation 30 is that simplifying risks, e.g., with the "Removing Identical Risks" rule, may result in the term remaining, with some amount of time associated with the Probability – Severity combination. The algebraic risk rule for simplifying risks by "Removing Unequal Risks" is useful for cleaning out probability – severity combinations with small amounts of time remaining.

### Uncertainty in the Benefit-Risk Analysis

Because the inputs to the Benefit-Risk Analysis have uncertainty intervals around them, the Benefit-Risk Analysis also has an uncertainty interval around its conclusion that the Benefit outweighs the Risk. Knowing this uncertainty interval can inform decisions about how much the Benefit-Risk Analysis decision can be trusted; e.g., if the uncertainty interval of each Table in Equation 9 is much smaller than the difference between the right and left sides of Equation 9, then conclusion of the Benefit-Risk Analysis can be trusted. Conversely, if the uncertainty interval of each Table in Equation 9 is much greater than the

difference between the right and left sides of Equation 9, then conclusion of the Benefit-Risk Analysis should can be questioned.

In at least one example, the Taylor Series can be used to approximate variation in the inputs to any one or more of the equations described above herein. Specifically:

$$\sigma_R^2 \approx \sum_{i=1}^k \left( \frac{\partial R}{\partial x_i} \right)^2 \sigma_{x_i}^2$$

*Equation 32*

As mentioned previously herein, the table look-up operation (e.g., for Equation 9) can be implemented as a table look-up with wide ranges for each value. Accordingly, the respective derivatives,  $\frac{\partial R}{\partial S_i}$  and  $\frac{\partial R}{\partial P_i}$ , may not be continuous functions. Therefore, in at least one example, the propagation of uncertainty is estimated using a Monte Carlo simulation of the variation in risk from the expected range of variation for  $S_i$  and  $P_i$  (and  $W_i$ , if applicable). This may require, in some instances, simulating the variation of all inputs simultaneously. Once the modeling of the variation of all the inputs to the equation is complete, a Monte Carlo simulation with 100 randomly chosen values from each input will, when these 100 sets of inputs are run through the equation, provide a reliable distribution of the variation by the risk of interest. Once the variation has been determined, the shape of the probability density function can be determined, and predictions can be made for any uncertainty range for hypothesis testing.

### Different patient populations

In at least another example, the benefit and/or risk of a particular medical product or procedure can be calculated for different patient populations using one or more of the methods described above herein. Special care should be taken with patient populations to ensure that the risks are based on data unique to these populations and ensure that any risks that are unique to, or absent from, this patient population are accounted for in the model of Patient Health. By noting the patient populations in which the benefits outweigh the risks, the range of populations that can use a medical product or procedure can be appropriately limited or increased.

### Multiple diseases

In at least another example, if a particular medical product or procedure can be and/or is intended to be used to treat multiple diseases, each disease may have its own Benefit-Risk calculation using one or more of the methods described above herein. Thus, the product or procedure can only be indicated for use for those combinations of diseases where the benefit exceeds the risk.

### Instructions for use (IFU)

Generally, the instructions for use (IFU) of a particular medical product or procedure should define how the product or procedure is indicated for use. Thus, in at least another example, the benefit should be shown to exceed the risk for each of the different indications for use. Such a process can reveal that different indications for use have different Benefit-Risk ratios. The calculated Benefit-Risk ratios for each indication can assist in defining when the product or procedure should be used despite the risks, and for which patient population.

### Customizing Risk Metrics for Risks for Emotion

Most medical products treat a patient's physical harms, and we are relatively comfortable with the Benefit-Risk analysis of these products. In contrast to this comfortable situation, some people are uncomfortable concluding that the benefits of a surgery whose goal is to improve someone's appearance outweigh the risks of that surgery. One of the strengths of this paper's structured approach to Benefit-Risk analysis is that it is adaptable, and this adaptability may help resolve the discomfort about the Benefit-Risk analysis of purely aesthetic medical procedures.

As mentioned above, Table 2 - Example of five qualitative **severity** levels and Table 3 - Example of five semi-quantitative **probability** levels come from TR 24971 as non-limiting examples of the tables that can be used to quantify the probability and severity of harm. It seems reasonable that part of the discomfort about the Benefit-Risk analysis of purely aesthetic medical procedures is that they are not 'fixing' a physical injury that can be fairly measured by the tables in TR 24971. Instead, the primary benefit of these procedures is the improved self-esteem of patients.

In order to account properly for benefits to the patient's improved self-esteem and self-image, Table 2 (Example of five qualitative severity levels) needs to be modified to account for mental risks instead of only physical risks. In order that the mental risks of aesthetic products and procedures is given proper weight, relative to the physical risks, we should step back from building risk metrics based purely on examples of purely aesthetic medical treatments. Because the benefits of purely aesthetic medical procedures get so tied-up in emotion, to avoid over (or under) emphasizing the mental benefits of purely aesthetic medical procedures, the severity table should be constructed based on a wider variety of products than only purely aesthetic products. For instance, non-aesthetic medical treatments with mental benefits and both mental and physical risks should be used, *together* with the benefits and risks of purely aesthetic products, to create more-appropriate probability and severity metrics than are in ISO 14971.

Non-aesthetic medical treatments with mental benefits and both mental and physical risks include various medical treatments (including drugs) to treat mental disorders ranging from anxiety to schizophrenia to manic depression. If we use non-aesthetic medical treatments like for diseases these, along with using purely aesthetic medical treatments like creams and surgeries, to construct 3 or 5 level severity tables that account for both mental and physical risks, we can create risk metrics for medical treatments that benefit our mental state are built with appropriate attention to both ego and safety.

As was discussed earlier, benefits and risks are traditionally stated in terms that make comparison difficult (e.g., the previously cited FDA guidance on Benefit-Risk Analysis). This difficulty is especially evident for a purely aesthetic medical product or procedure whose benefit lies in the mismatch of a purely mental benefit vs. risks that are both physical and mental. However, just as the method disclosed in this paper makes the Benefit-Risk Analysis of other products more objective, we can also use this method to make the Benefit-Risk Analysis of purely aesthetic medical treatments more objective.

### Models of patient health

In at least one example of the present disclosure, a model for patient health is disclosed. The methods described herein enable us to measure the amount of benefit and risk from a product or procedure significantly more objectively than has been possible in the past. Taken together, these benefits and risks create a significantly more-objective measure of the health of a patient population than has traditionally been done.

Once built, this model can be built and used to compare the rate of various risks to the patient population of the product or procedure. Changes to the patient's health can come from the product or procedure's intended action, can come from a side effect of the product or procedure, or can come from the patient

population's underlying health concerns; i.e., the changes may be unrelated to the product or procedure. In at least an additional example, the Patient Health model can be extended to include these factors using Bayesian statistics. For instance, comorbidity factors can be included for the patient population and their likely impact on the health of the patient population.

An advantage of extending the model to include such factors is that it enables reliable comparisons of predicted and actual rates of occurrence. Such comparisons can be especially useful with respect to occasional harmful events (e.g., a heart attack or allergic reaction). If the model is accurate with respect to known diseases and effects, and if the rates of occasional harmful events are different from the actual rate by statistically significant amounts (which may be determined by calculating one or more uncertainty intervals as described herein), then the difference can be attributed to the medical product or procedure under consideration. Otherwise, the side effect is presumed to be due to random chance and has no causal connection to the product or procedure.

In at least an additional example, the calculated rate of side effects is accompanied by a calculated confidence interval.

The model can be extended to include multiple disease states. The model may also include, for instance, the comorbidity factors discussed above. In the above equation, if  $D$  represents the set of disease states of patients treated with the medical product or procedure, then  $l = n(D)$  refers to the number of disease states treated with the product or procedure,  $S_j^i$  represents the severity rating of the  $j^{\text{th}}$  harm of the  $i^{\text{th}}$  disease state,  $m_i = n(S_j^i)$  represents the number of harms caused by the  $i^{\text{th}}$  disease state,  $P_j^i$  is the probability rating of the  $j^{\text{th}}$  harm occurring at the severity  $S_j^i$  for the  $i^{\text{th}}$  disease state,  $W_j^i$  is a time factor (e.g., as discussed above herein) for the  $j^{\text{th}}$  harm of the  $i^{\text{th}}$  disease state, and  $R$  is the likely amount of risk to the patient's health from the medical product or procedure. As a non-limiting example, if a user uses the 7x5 table from ISO 14971, then  $P_j^i \in \left\{ \begin{array}{l} \text{Expected, Often, Frequent, Probable,} \\ \text{Occasional, Remote, Improbable} \end{array} \right\}$  and  $S_j^i \in \left\{ \begin{array}{l} \text{Negligible, Minor, Serious/Major,} \\ \text{Critical, Catastrophic / Fatal} \end{array} \right\}$ . With these assumptions, the risk to the patient from the medical product or procedure is:

$$R = \left\{ \begin{array}{l} (P_1^1, S_1^1, W_1^1), (P_2^1, S_2^1, W_2^1), (P_3^1, S_3^1, W_3^1), \dots, (P_{m_1}^1, S_{m_1}^1, W_{m_1}^1), \\ (P_1^2, S_1^2, W_1^2), (P_2^2, S_2^2, W_2^2), (P_3^2, S_3^2, W_3^2), \dots, (P_{m_2}^2, S_{m_2}^2, W_{m_2}^2), \\ (P_1^3, S_1^3, W_1^3), (P_2^3, S_2^3, W_2^3), (P_3^3, S_3^3, W_3^3), \dots, (P_{m_3}^3, S_{m_3}^3, W_{m_3}^3), \dots, \\ (P_1^l, S_1^l, W_1^l), (P_2^l, S_2^l, W_2^l), (P_3^l, S_3^l, W_3^l), \dots, (P_l^1, S_l^1, W_l^1) \end{array} \right\}$$

Equation 33

Similar to Equation 33, risk models for both  $R_A$  and  $R_B$  can be built to represent complete models of patient health. In at least a further example, the model considers synergistic effects from multiple exposures with the medical product or procedure. See also ISO 31010, Section 6.3.5.1.

In at least one example, the model is generated by determining the typical characteristics of a patient suffering from one or more diseases or conditions that the medical product or procedure under consideration is designed to treat. Such a determination could be made by identifying one or more diseases or conditions the medical product or procedure is intended to treat, and estimating, using medical data (e.g., published data, including, for instance clinical data) regarding the disease characteristics, the patient's likely state of health. Such an estimate may include, for example, determining how the disease will likely harm the patient, the probability of such harm occurring, the duration of harm, and whether the harm will occur immediately or at some point in the future.

### Benefit-Risk Analysis for Compliance / Product Availability

Given the central role that Benefit-Risk Analysis has as a final check before releasing new products to market, it should be no surprise that Benefit-Risk Analysis is also a key indicator of product compliance (i.e., compliance with regulations) and availability (i.e., whether field actions are required)<sup>3</sup>.

Before this structured approach to Benefit-Risk Analysis, the tables in TR 24971 were useful only for relative measures of risk, but their absolute value meant nothing. The strength of the method of determining whether benefit exceeds risk is that the measures of risk are compared with measures of benefit, which gives the absolute value of the risk tables meaning. A company, or regulator, can review the original Benefit-Risk Analysis and see if post-market circumstances have changed the original analysis significantly.

Looking at changes to the Benefit-Risk Analysis can be useful when assessing the criticality of audit observations. If a production line is cited for compliance problems because it was not sufficiently clean, the risks to patients from a dirty production line can be increased to reflect the audit finding. If increasing these risks changes whether the product's risk profile sufficiently that the product's risks exceed the benefits, then the non-compliant stock clearly needs to be withdrawn from the field. Conversely, if increasing these risks to patients as far as possible does not change the fact that the product's benefits outweigh its risks, then this argument would favor not taking any field action.

In addition, per Section 7.4.1 of ISO 14971, "An important consideration is whether an anticipated benefit can be achieved through the use of alternative solutions without that risk or with smaller risk. This involves comparing the residual/ risk for the manufacturer's medical device with the residual/ risk for similar medical devices." Therefore, it is possible that, although an audit observation (or a combination of observations) does not increase risk to the patient sufficiently that the product's risks exceed the benefits, those same observation(s) may increase the risk sufficiently that, per Selecting the Best Therapy from a List of Alternative Therapies, the increase in risk results in the conclusion that the non-compliant stock still needs to be withdrawn from the field – but the withdrawal is because a different product provides better therapy and not because the audited product's risks exceeds its benefits.

### Summary of Applications

This paper contains a non-limiting example of applications of its method to determine whether the Benefit of a medical treatment exceeds the Risk. This method's ability to systematically determine if benefit exceeds risk opens up numerous applications, some of which build on each other to create additional applications.