

Benefit-Risk Determination: A Quantitative Approach

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Summary

The Medical Device Regulation (2017/745) (MDR) has made clinical benefit and the quantitation of benefit-risk critical parameters in the demonstration of conformity to Regulations. ISO 14971: 2019 has also put increased emphasis on the evaluation of clinical benefit. While ISO 14971 includes informative annexes on the quantitative and qualitative evaluation of risk, it does not provide the same for quantifying clinical benefit. In the absence of relevant guidance on specific methodology, manufacturers are facing challenges with respect to how to evaluate and effectively quantify benefit-risk, and therefore appropriately demonstrate compliance with the Regulations.

Consequently, benefit-risk analyses have been purely qualitative (and middling at best), to date, despite the regulatory requirement of a quantitative benefit-risk ratio. Provision of a quantitative assessment tool can reduce some of the subjectivity that is inherent in a qualitative argument. This white paper will suggest a methodology and associated examples that have successfully gone through notified body review to address this critical need.

Introduction

Persistent risk management concerns as a notified body (NB) reviewer

During his career as a notified body reviewer, Jaishankar Kutty, Ph.D., frequently observed that manufacturers use the same risk acceptability chart for all devices, even though the acceptable risk levels for different device classes must obviously be different. Per the standard, the definition of risk comes under the risk management plan, which can be different for each device/device family, thus offering a method for differentiating risk acceptability for different types of products from the same manufacturer. Also, many manufacturers incorrectly used risk priority number (RPN) from earlier editions of failure modes and effects analysis (FMEA) as a technique to establish risk acceptability. Risk analyses have been the forte of the automotive and airline industries, and they have discontinued use of the RPN technique due to the related inaccuracies and limitations hindering product development and process improvement activities. The medical device fraternity is not far behind. For example, instead of having Acceptable Risk and Unacceptable Risk regions defined by policy (clause 4.2 of per ISO 14971:2019 and ISO TR 24971:2020), several manufacturers have incorrectly identified an intermediate region as As Low As Reasonably Practicable (ALARP).

In practice, ALARP is not a region on the risk acceptability chart but is in fact an approach towards identifying the risk reduction process. The current ISO 14971:2019 attempted to correct this inaccurate interpretation, wherein, the middle region is more correctly an Investigate Further Risk Control region per figure C1 of ISO TR 24971:2020. Consequently, the risks that appear in this region of the risk chart should be further reduced by applying additional risk mitigation measures. Following the publication of ISO 14971:2012, there has been widespread confusion in the EU about acceptable versus unacceptable risks.

Per EN ISO 14971:2012, manufacturers could no longer use the ALARP approach instead requiring them to reduce risk using the As Far As Possible (AFAP) approach, which was deemed to be in accordance with the medical device directive in the EU. However, this harmonized version of the standard (2012 version) did not identify a process for identifying AFAP levels. Moreover, currently, EN ISO 14971:2012 version has been withdrawn by CEN with the release of EN ISO 14971:2019, and the 2019 version of the standard still does not identify a process for identifying AFAP levels. Ultimately, providing objective evidence of risks reduced to AFAP levels to the regulators became an elusive effort since a decision of how much improvement is enough has always been subjective. A simple way to circumvent this issue is to document the rationale for why a certain residual risk is considered reduced to AFAP levels in terms of its impact to the clinical evaluation considering patient safety, device performance and expected clinical benefits.

Importantly, the requirement of mitigating/controlling risk allowed the use of benefits afforded to the patient or "benefit" as an alternative method of placing a medical device on the market when a residual risk was evaluated as "unacceptable" by risk management activities. The medical device must not be put on the market if the benefit does not outweigh the risk in a clearly quantified and documented benefit-risk analysis. The NB reviewers and their regulators are focusing significant scrutiny on the benefit-risk ratio as part of the benefit-risk analysis/benefit-risk determination since a manufacturer must not place a device on the market unless the benefit outweighs the risk or until further risk reduction is applied.

Benefit-risk under the new regulations

Clarity on this situation in the EU has not improved much with the advent of the MDR, which requires manufacturers to reduce risks AFAP, without impacting the benefit-risk ratio. The MDR refers to the benefit-risk ratio as benefit-risk determination and benefit-risk analysis interchangeably. Historically, the benefit-risk determination has been an idea associated with pharmaceuticals, which is now borrowed heavily both by the MDD and the MDR. In ISO 14971, the term 'risk-benefit' was used in the 2000 and 2007 versions of the standard. However, in the latest 2019 edition of the standard, the term has been revised to 'benefit-risk' since regulators found that manufacturers were only evaluating benefit as an afterthought, and hence wanted to emphasize benefit ahead of risk. The MDR defines benefit-risk determination in Article 2 (24) as the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer.

Other than that, unfortunately, the regulation does not define what an acceptable benefit-risk determination is or discusses how to accomplish reaching the AFAP level for each residual risk. Benefit is defined in ISO 14971:2019 3.2, as positive impact or desirable outcome of the use of a medical device on the health of an individual, or positive impact on patient management or public health. The definition of benefit in the MDR Article 2 (53) is the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

The NB reviewers' and regulators' interpretations of these definitions in combination with the requirement to specify the expected clinical benefits in the instructions for use per GSPR 23.4 (c), is a quantitative benefit-risk analysis culminating in a quantitative benefit-risk ratio with a clear acceptance criterion defined. This quantitative benefit-risk ratio is expected to set the baseline in terms of device residual risk profile, against which all future device modifications and generational changes will be evaluated in terms of impact to the clinical evaluation. ISO TR 24971:2020 section 7.4 provides numerous examples of benefits and benefit-risk analyses. However, none of these examples help in establishing a quantitative benefit-risk ratio. This paper aims to tackle a very troublesome and often caliginous topic for many medical device companies. We present an intuitive method to quantitatively determine a benefit-risk ratio for medical devices based on the fundamental principles of risk management commonly understood in the industry.

Determining Benefits and Risks

Of primary importance in evaluating the benefit-risk ratio is to define the relevant and appropriate risks and benefits for the device when used as intended. Of course, the goal of almost any medical device is to improve patient health with minimal patient harm, but the specific improvement in patient health and the specific possible harms must be identified. In addition, forming outcomes that are specific in nature, they must also be measurable. To compare a patient's health before and after treatment or compare one device to the next, measurements must be done to quantify the impact of the device. Determining these specific and measurable outcomes (SMOs) is integral to a rigorous quantitative analysis of benefit-risk.

In an effort to illustrate specific steps in developing a benefit-risk analysis, consider an anonymized wound dressing, AdBan. The clinical evaluation of AdBan is aligned with the product's instructions for use and risk management documentation, which detail the information provided in the table below.

Intended Use	AdBan Wound Dressing provides a moist environment for the management of partial and full thickness wounds.
Indications for Use	1st and 2nd degree burns Traumatic wounds Surgical wounds Pressure ulcers Leg ulcers Diabetic foot ulcers
Performance Outcomes	Duration of adhesion Moisture level of wound environment Reduction of wound size
Benefits	Wound healing
Residual Risks	Allergic reaction Periwound maceration Skin damage on removal

Benefits

Identifying the clinical benefits is a nuanced undertaking. For a device with more than one positive impact, multiple benefits would be defined. Clinical benefits may or may not correspond one-to-one with the performance measures of the device. Moreover, clinical benefits are expected to be discussed from the perspective of the patient or user or in terms of patient management per the definition in Article 2(53) of the MDR. As defined in the MDR and interpreted in *Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation* (MDCG 2021-6), performance and benefit can be differentiated as follows:

Performance	The ability of a device to achieve its intended purpose
Clinical Performance	The ability of a device to achieve its intended purpose, thereby leading to a clinical benefit
Clinical Benefit	The positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s)

The clinical evaluation may include a discussion of multiple performance outcomes that demonstrate the ability of the device to achieve its intended purpose. Outcomes related to the mechanical properties of the device provide evidence for performance, however, they are not always related to the clinical benefit. It may be the case that only a subset of the performance outcomes will be considered for the benefit-risk ratio. Patient-related clinical benefits tend to be discussed mostly in measurable terms of improvements in quality of life, symptom relief, pain relief, reduced rates of re-interventions, improved patient management type outcomes such as enhanced diagnosis (for imaging devices) and technical success in the facilitation of index procedures (for surgical accessory-type devices).

Consider the AdBan example:

Performance Outcomes	Duration of adhesion Moisture level of wound environment Reduction of wound size
Benefits	Wound healing

Performance outcomes may also serve as surrogate measures of clinical benefit. These provide the specificity required for an SMO.

Performance Outcomes	Reduction of wound size
Benefits	Wound healing

In summary, the benefit outcomes should tell the story of clinical improvement that the device under evaluation provides to the patient.

Risks

Identifying potential risks is commonplace with conformity to the requirements of ISO 14971 and the MDR GSPRs 1,2,3,4,5 and 8. The standard defines risks as the frequency of occurrence of a harm combined with the severity of the harm; the harm being injury or damage to the health of the patient. For this document, the term *risk* is used to refer to both *harm* and *risk* as defined in ISO 14971. References to frequency of occurrence and severity of the risk will also be made.

Risks identified for the device in the clinical evaluation should align with the risk management file and other available risk documentation. For complex devices, however, it may become unruly and unnecessary to include all potential risks from the hazard analysis. The most common harms, including those identified in the IFU and those reported in clinical studies using the device, should be included in the analysis. In an ideal situation, only risks attributed to the device under evaluation would be included in the analysis. Consider the AdBan example, *allergic reaction* and *skin damage on removal* can reasonably be attributed to the device.

Risks	Allergic reaction Periwound maceration Skin damage on removal
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In practice, a definitive cause is less likely to be assigned to each harm. A clinical study of AdBan reported bleeding and infection among the included patients. Although bleeding would most likely be related to the patient condition, infection is more ambiguous. Infection very often is multifactorial and could have been present prior to treatment or infection could have been the result of a contaminated bandage. In this case, bleeding can be reasonably excluded, but it would be prudent to report infection as a possible risk. Any adverse events reported that could reasonably be associated with the use of the device should be considered in the benefit-risk analysis.

Risks Attributed to the Device	Allergic reaction Periwound maceration Skin damage on removal
Other Risks	Bleeding Infection

Ultimately, for each device, one or more clinical benefits and one or more risks will be identified. These items should be specific and measurable in nature and represent the intended use of the device on the intended patient population.

Currently, we have chosen to focus on the most important risks (not every residual risk in the IFU) and most important benefits since our main aim is to discuss quantitation of benefit-risk. During an actual clinical evaluation review, the reviewers will expect to understand the benefit-risk analyses stratified by patient population.

For instance, in the subject AdBan example, we have not discussed aspects related to the patient population and the medication regimen. These items can significantly impact the wound healing related outcomes in diabetic patients and those on chronic anticoagulation regimens. Such nuances along with the breadth of indications will be critical considerations in any benefit-risk analyses.

Evaluating Benefits and Risks

To determine overall benefit and risk for a device, both the magnitude and the frequency of occurrence must be considered. In other words, we aim to answer the following key questions:

How great is the benefit?

How many people experience it?

Similarly, how severe is the risk, and how many people experience it?

The need to combine both of these measures is succinctly described in *Clinical Evaluation: A Guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC* (MEDDEV 2.7/1, Rev. 4, A7.2) which states, “A large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of subjects.” Again, benefits and risks defined in a specific and measurable manner allow these outcomes to be evaluated.

Frequency of Occurrence

Frequency of occurrence in the population is measured by how many patients experience the event. In a straightforward case, the SMO would already express the number of patients that experienced the benefit.

Risk

Allergic reaction (measured by % of patients that experienced an allergic reaction)

However, not all outcome measures can be simply reported in this manner. In some cases, additional interpretation is necessary to determine the number of patients that achieved a specific level of benefit or risk, involving thresholds or intervals. For example, consider the benefit of wound healing as measured by a reduction in wound size. Assuming a reduction of at least 5 mm² in the surface area of the wound is clinically relevant, this threshold can be considered for establishing the frequency of occurrence.

Benefit	Wound healing (measured by reduction in wound size)
Benefit reported as frequency	% of patients that experienced a reduction in wound surface area $\geq 5 \text{ mm}^2$

Magnitude and Severity

The magnitude of each clinical benefit and the severity of each risk are essential factors to include in overall benefit and risk values. At first consideration, some outcomes appear well suited to a direct measure of magnitude. For example, the decrease in wound surface area (measured in mm²) indicates the magnitude of wound healing and the amount of blood loss (measured in mL) indicates the severity of bleeding. Direct measures, however, do not necessarily provide clinically relevant information. A 5 mm² reduction in wound surface area may be much more beneficial than a 5 mL loss of blood is severe. This paper proposes a novel method to measure that achieves the following:

1. Assign magnitude and severity values for outcomes lacking these implicit measures; and
2. Establish a normalized scale so that benefit and risk can be directly compared.

Determining magnitude values is a more subjective task than calculating the of frequency of occurrence. To reduce subjectivity and bias, this proposed method assigns magnitude values based on the established risk documentation. Severity of harms will be included in an ISO 14971:2019 compliant risk analysis. The scale of severity values typically ranges from 1 to 5, and a description is assigned to each value. Magnitude of benefit values can subsequently be determined by creating an analogous scale. The table that follows provides an example.

Magnitude	Risk (Harm severity)	Benefit
1	Inconvenience/annoyance	Prevention of an inconvenience/annoyance
2	Temporary injury or impairment not requiring medical intervention	Prevention of temporary injury or impairment not requiring medical intervention Absence of benefit would lead to temporary injury or impairment not requiring medical intervention
3	Injury or impairment requiring medical intervention	Prevention of injury or impairment requiring medical intervention Absence of benefit would lead to injury or impairment requiring medical intervention
4	Permanent impairment or life-threatening injury	Prevention of permanent impairment or life-threatening injury Absence of benefit would lead to permanent impairment or life-threatening injury
5	Patient death	Life-saving

With the use of this scale, magnitude values will be the same for analogous benefit-risk pairs. For example, the benefit of *wound healing* will be assigned the same magnitude as the risk of *wound deterioration*, allowing for normalized benefit and risk values.

In practice, ambiguous cases are bound to emerge. In these cases, it is prudent to assign the highest severity level to ambiguous risks and the lowest magnitude level to ambiguous benefits, presenting a worst-case scenario benefit-risk ratio. **Use of this method prioritizes patient safety and reduces manufacturer bias in benefit-risk calculations.**

As an example, consider bleeding. Reports of bleeding in clinical literature may not specify or differentiate between *minor bleeding*, *major bleeding*, and *severe bleeding*, which may all be assigned distinct severity levels in the risk documentation.

AE reported in the literature	Harm reported in the risk file	Severity of harm
Bleeding	Minor bleeding	Risk severity 2
	Major bleeding	Risk severity 3
	Severe bleeding	Risk severity 4

When reports of bleeding appear in the literature, it is necessary to interpret the level of bleeding from the author's description. Were minor adverse events reported? Was intervention needed to control the bleeding? If insufficient information is available to answer such questions, the most conservative decision is to assign bleeding a severity of 4.

This novel method of assigning magnitude and severity levels allows for a normalized comparison of benefits and risks. It also decreases the risk of bias, particularly bias in favor of the manufacturer, which allows for a more rigorous and convincing argument for a favorable benefit-risk ratio.

Evaluating a Benefit-Risk Ratio

Benefit Values, Risk Values, and the Benefit-Risk Ratio

Once frequency and magnitude are assigned for each benefit and risk, their product is taken as the quantification of a benefit value and a risk value for each. Once these values are calculated, a simple benefit-risk ratio is calculated.

$$\begin{aligned}\text{Benefit Value} &= \text{Frequency} \times \text{Magnitude} \\ \text{Risk Value} &= \text{Frequency} \times \text{Severity} \\ \text{Benefit-Risk Ratio} &= \frac{\text{Benefit Value}}{\text{Risk Value}}\end{aligned}$$

In Defense of the Pairwise Comparison

Note that this method provides a value for each benefit and each risk; it does not combine all benefits nor all risks to establish one singular benefit value and one singular risk value. As a result, a pairwise comparison of each benefit to each risk is calculated. Although summarizing benefits and risks to singular values would certainly present a clean summary with a singular benefit-risk ratio for the device, such a method would lose the granularity that allows for an in-depth analysis of benefit and risk.

Of particular interest are risks with a high level of severity. Consider a case with many risks of severity 1 and 1 risk of severity 5. Any unfavorable outcomes associated with the high-severity risk may be obscured by the multitude of low-severity risks. It is more valuable to consider each high-severity risk on its own, which allows for a transparent and comprehensive reporting of the benefit-risk profile.



Determining Acceptability

Pre-defined acceptance criteria are integral in establishing a rigorous argument for the favorability of the benefit-risk ratio. In the most basic of terms, any benefit-risk ratio greater than 1 is favorable (i.e., the benefit value is greater than the risk value). The MDR, however, specifies that when weighing risks against benefits the generally accepted state of the art must also be taken into consideration. Using the same methodology described in this paper, benefit-risk ratios can be calculated for the generally accepted state of the art including similar devices and/or alternative therapies.

These results will allow for a direct benefit-risk ratio comparison between the device under evaluation and other treatment options available to the patient. To achieve favorability in comparison to the generally-accepted state of the art, the benefit-risk ratio for the device under evaluation will be greater than that of state of the art devices. Determining acceptance criteria becomes more complicated when a device has multiple benefits and multiple risks, resulting in a collection of benefit-risk ratios—1 for each benefit-risk pair.

This paper sets out to describe options and considerations for acceptance criteria, however criteria for each device may be unique in order to address the specific characteristics of the device and target patient population. Perhaps the most straightforward criterion would specify that the benefit-risk ratio should be greater for the device under evaluation than for the state of the art for at least half of the benefit-risk pairs. Another consideration may be dependent only on benefits or risks of a certain magnitude. For example, the benefit-risk profile would only include a comparison of benefit-risk ratios involving risks of severity 4 and 5. Ultimately the acceptance criteria must be determined prior to calculating any benefit and risk values and justified in an unbiased manner.

Alternative Methods

The steps presented in this paper present one method of calculating a benefit-risk ratio; however, other methods of quantitation are available. Calculating a number needed to treat/number needed to harm (NNT/NNH) is more often used in pharmaceutical trials, but they can be adapted for medical device trials as well. This analysis informs on the number of patients that need to be treated with the device under evaluation to provide a benefit (or cause a harm) above and beyond what the patient would experience with the alternative. This method provides an inherent comparison to the state of the art, typically no treatment, but it only provides information on the frequency of occurrence. Additional steps must be taken to account for the magnitude of benefits and the severity of harms. While these values provide intuitive interpretations of frequency, that intuition is lost when factoring in severity and calculating benefit-risk ratios, particularly in cases of multiple benefit or risks.

The quantitative benefit-risk ratio may not be suited to every device, however, a robust benefit-risk analysis can still be conducted. Information on safety and clinical performance of a medical device is provided by multiple sources—clinical trials, published articles, post-market activities, etc., resulting in multiple values for each outcome. The methodology presented in this paper, however, demands the data be summarized so that each benefit and each risk has one value rather than a range of values. A meta-analytic pooled average of the available data is the most rigorous and appropriate method to quantitatively summarize the outcomes from a variety of sources. However, depending on the clinical heterogeneity of the available studies, including patient condition and follow up times for example, a meta-analytic approach may not be appropriate.

A qualitative approach to the benefit-risk assessment is acceptable under MDR as long as it is appropriately justified. Reviewers will expect the qualitative analyses to be a discussion of the quantitative assessment of clinical benefits in comparison with the residual risks. Qualitative analyses can be rigorous and, although not as succinctly, can prove the favorability of the benefit-risk profile in relation to the generally accepted state of the art.

This approach may be dependent on within-study comparisons of the device under evaluation to similar devices or alternative therapies, with conclusions of these studies summarized qualitatively. Alternately, the safety and performance outcomes can be reported as ranges of values for both the device under evaluation and devices that represent the state of the art. While the ranges may overlap, they would drive the discussion of benefits and risks. Whatever approach is used, all data, favorable and unfavorable, must be discussed. Generally, the manufacturer should highlight the favorable data while thoroughly acknowledging and reporting the unfavorable data. Ultimately, a sound justification must be made to capture the acceptability of the benefit-risk profile.

Conclusions

The MDR and ISO 14971 provide a paucity of guidance on calculating or providing a rigorous justification for the benefit-risk ratio of a medical device, despite the predominant role this ratio plays in showing conformity with the GSPRs and, ultimately, allowing for placement on the market. This paper has provided a straightforward, intuitive method to quantify the benefit-risk ratio based on safety and performance outcomes of the device under evaluation, taking into account the generally accepted state of the art.

RQM+ has successfully implemented this approach to satisfy requests for quantitative benefit-risk analysis from BSI. The following is an anonymized real-life example of how to implement this approach through risk management and clinical evaluation.

[Contact RQM+](#) for support with benefit-risk quantitation as well as implementation of all elements of the MDR.

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Appendix: Example

This section provides a step-by-step guide through the benefit-risk ratio calculations using an anonymized wound dressing (AdBan) as the device under evaluation.

Prior to initiating an analysis, the acceptance criteria for favorability of the benefit-risk ratio must be determined. For this example, AdBan is considered to have a favorable benefit-risk ratio in, taking into account the state of the art (SOTA) when the following criteria are met:

1. The benefit-risk ratio for AdBan is greater than the benefit-risk ratio for SOTA for at least half of the benefit-risk pairs; and
2. The benefit-risk ratio for AdBan is greater than the benefit-risk ratio for SOTA for any benefit-risk pairs that include a risk of severity 5.

To begin the analysis, the benefits and risks are determined. (Examples in the text above are repeated here.)

Benefits	Wound healing
Risks	Allergic reaction Periwound maceration Skin damage on removal

These outcomes are re-defined in a specific and measurable manner.

Benefits	% of patients that experienced a reduction in wound surface area $\geq 5 \text{ mm}^2$
Risks	% of patients that experienced an allergic reaction % of patients that experienced periwound maceration % of patients that experienced skin damage on removal % of patients that experienced infection

Data are gathered from clinical trials and published clinical studies reporting on these specified outcomes. This evidence is collected for both the AdBan as well as the state of the art. Based on practice guidelines and clinical recommendations, the current state of the art is deemed to be other similar wound dressings. Results reported for these specific and measurable outcomes are pooled using meta-analytic methods.

Frequency of occurrence measures are summarized by calculating a pooled prevalence. Due to clinical and methodological heterogeneity among most of the published literature on AdBan, a random effects model is often the appropriate choice for pooled calculations. Pooled prevalence methods also allow for the inclusion of uncontrolled clinical studies, which facilitates the inclusion of all relevant use of AdBan rather than just use in controlled studies. Although the use of uncontrolled studies eliminates the possibility of calculating an odds ratio or risk ratio, comparison to the state of the art is instead made with the quantitative benefit-risk ratio.

The following table presents the results of pooled prevalence calculations, which serve as the frequency of occurrence values for the benefits and harms.

	Specific Outcome	Results for AdBan	Results for State of the Art
Benefits	Reduction in wound surface area $\geq 5 \text{ mm}^2$	65.0%	62.2%
Risks	Allergic reaction	5.2%	4.1%
	Periwound maceration	1.2%	1.3%
	Skin damage on removal	0.4%	0.6%
	Infection	2.3%	0.7%

All of the adverse events reported, allergic reaction, periwound maceration, skin damage on removal, and infection, are accounted for in the risk management file for AdBan. The appropriate severity level for each is assigned.

Note that the risk management file for AdBan includes both localized infection (severity 3) and systemic infection (severity 4). Based on descriptions in the literature, it is determined that all of the allergic reactions reported were localized in nature; therefore, this risk is assigned a severity level of 3.

Risk Severity	Allergic reaction	3
	Periwound maceration	3
	Skin damage on removal	2
	Infection	3

The magnitude of the benefit is determined next. AdBan is indicated for minor wounds requiring intervention; therefore the benefit of wound healing (as measured by wound size reduction) is assigned a magnitude level of 3, pertaining to injury or impairment requiring medical intervention.

Benefit Magnitude	Wound healing (Reduction in wound surface area $\geq 5 \text{ mm}^2$)	3
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Based on the reported frequency of occurrence and the assigned magnitudes, the benefit value and risk values are calculated.

Benefit Value = Frequency x Magnitude

Risk Value = Frequency x Severity



Note that frequency of occurrence percentages are converted to decimals.

	Specific Outcome	Magnitude	Frequency AdBan	Value Adban	Frequency SOTA	Value SOTA
Benefits	Reduction in wound surface area $\geq 5 \text{ mm}^2$	3	0.650	1.95	0.622	1.866
Risks	Allergic reaction	3	0.052	0.156	0.041	0.123
	Periwound macerataion	3	0.012	0.036	0.013	0.039
	Skin damage on removal	2	0.004	0.008	0.006	0.012
	Infection	3	0.023	0.069	0.070	0.210

The benefit values and risk values are then used to calculate benefit-risk ratios for each benefit-risk pair.

$$\text{Benefit-Risk Ratio} = \frac{\text{Benefit Value}}{\text{Risk Value}}$$

In this case there is 1 benefit and 4 risks, resulting in 4 benefit-risk pairs.

In this case there is 1 benefit and 4 risks, resulting in 4 benefit-risk pairs.

Benefit	Risk	Benefit Value AdBan	Risk Value AdBan	B-R Ratio AdBan	Benefit Value SOTA	Risk Value SOTA	B-R Ratio SOTA
Reduction in wound surface area $\geq 5 \text{ mm}^2$	Allergic reaction	1.950	0.156	12.50	1.866	0.123	15.17
	Periwound maceration	1.950	0.036	54.17	1.866	0.039	47.85
	Skin damage on removal	1.950	0.008	243.75	1.866	0.012	93.3
	Infection	1.950	0.069	28.26	1.866	0.210	8.89

Pulling out the benefit-risk ratios for AdBan and for the SOTA, it is clear that 3 out of 4 benefit-risk ratio pairs show that AdBan is more favorable than the SOTA, thereby meeting the acceptance criteria.

Benefit	Risk	B-R Ratio AdBan	B-R Ratio SOTA	B-R Ratio AdBan > B-R Ratio SOTA?
Reduction in wound surface area $\geq 5 \text{ mm}^2$	Allergic reaction	12.50	15.17	N
	Periwound maceration	54.17	47.85	Y
	Skin damage on removal	243.75	93.3	Y
	Infection	28.26	8.89	Y

Although the acceptance criteria are met, it would be prudent to discuss the higher rates of allergic reaction in AdBan using the following considerations:

- **How many studies reported allergic reactions, and what was the level of evidence for each?**
- **Were within-studies comparisons of allergic reactions statistically significant between study arms?**
- **How quickly were allergic reactions resolved?**
- **Did the presence of an allergic reaction delay wound healing?**

Addressing the unfavorable outcomes help to complete the story of safety and performance, creating a thorough analysis of the benefit-risk profile.

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