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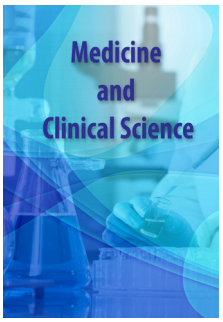
Mini Review



The Search for Safety: A Proposed Framework Based upon Insights from Clinical Research

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Abstract

Despite extensive investments of time, money, and work by regulatory bodies and the pharmaceutical industry, there is no widely accepted framework for the evaluation of the benefits and risks of medications. Not surprisingly, the current frameworks proposed by those two stakeholders are quite complicated and not readily accessible or understandable by one of the primary, intended beneficiaries of such information – the patient.

What is desperately needed is a relatively simple tool that can be improved over time and that can be easily wielded by healthcare professionals and patients alike.

By drawing upon several concepts from clinical research it may be possible to express the benefit-risk evaluation as a mathematical model, a ratio of four derivable variables.

$$\frac{\text{Frequency x Weight of Benefit (Variable 3) x Disease Severity (Variable 4)}}{\text{Frequency of Adverse Reaction (AR (Variable 1) x Severity of AR (Variable 2)}}$$

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One of the many challenges facing modern medicine is the development of a benefit-risk assessment for medications that is not only widely accepted but also easy to use both by patients and health care providers. Incredibly, no such tool exists.

The definition of a "safe" medication will vary widely from individual to individual. Among patients with some direct or secondary experience, there will be an entire spectrum of responses. Someone may say, "Oh, it's a good drug. It has kept my aunt alive for years." Or a person may exclaim, "That drug killed my uncle." Or another may say, "It's an OTC medication. So, it has to be safe." Or someone else may even say, "It's FDA approved, so it must be safe."

On the other hand, patients may do some online research. There are, in fact, an increasing number of sites that do offer reliable information regarding potential side effects of medications. For example, one site, FactMed, states: "Our online community helps both patients and physicians accurately research and assess the risks and benefits for more than 20,000 different pharmaceutical products."1 One of the critical challenges for the consumer, however, is that there is no readily available way to determine the validity or applicability of the information provided at most sites. Performing unsubstantiated "research" is like attempting to get from a fire hydrant a small sip of water which may or may not be contaminated.

Some patients may turn to the package insert or to information provided by the pharmacy. For instance, after reading the package insert on a statin, a patient may ask with horror if the physician is trying to kill him. There are usually two conditions that lead to such a question. A patient may assume that he will experience each and every "side-effect" listed and not even consider if that particular side-effect is occurring any more frequently than with the placebo. Secondly, most also overlook the benefit of taking the medication, which is another way of saying that they overlook the risk of not taking it. If the patient does not perceive or believe the problem that the physician is trying to address with a medication, then the patient will understandably resist. That patient is solely focused on the fact that every medication has a potential "downside" and does not appear to even consider that everything has an associated risk, even not doing something, in this case, not taking a needed medication.

Therefore, considering only the "absolute safety" of a medication is only half of the equation. What is really needed is the benefit-risk assessment - how likely is it that the medication will help versus how likely is that it will hurt in some way. These two, simple questions are, in fact, incredibly complicated and remarkably difficult to answer.

Suppose this question of safety is posed to physicians from whom patients routinely expect a considered opinion.

Physicians, however, rely on the same processes as everyone else – past experience (referred to as clinical expertise) and research. Integrating these two processes along with the patient's input has now been formalized in the movement known as evidence-based practice (EBP), also referred to as evidence-based medicine. David Sackett, the founder of this movement, described it as "the integration of clinical expertise, patient values, and the best research

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evidence into the decision-making process for patient care. Clinical expertise refers to the clinician's cumulated experience, education and clinical skills. The patient brings to the encounter his or her own personal preferences and unique concerns, expectations, and values.

The best research evidence is usually found in clinically relevant research that has been conducted using sound methodology."2 The integration of these three components is, of course, not novel. What sets EBP apart is the vigor and thoroughness with which the research is reviewed and stems from the understanding that the quality of research may vary markedly from study to study. Further, treatment decisions are not ideally based upon the results of a single study, even one conducted well. Important treatment decisions are preferably based upon systematic reviews and meta-analyses that review and summarize the results of multiple, well-conducted studies.

It is important to note that EBP does not discount, or even de-emphasize, the importance of the physician's clinical expertise. In any single patient encounter, there are frequently multiple, complicated treatment decisions to be made. Clinical expertise and the patient's input are essential components especially in those situations where the body of research evidence is less than compelling.

If a physician is, in fact, considering prescribing a medication, recently approved by the U.S. Food & Drug Administration (FDA), there are additional hurdles. In general, the body of research evidence is less complete with newer medications as compared to older medications.

In such a situation, the physician will also have less clinical experience. Despite a certain amount of reluctance, the physician may feel the need to try a new medication in those situations where alternative, effective treatment is limited or nonexistent. He then will do some research, including a review of the prescribing information, and present the pertinent information to the patient. Package inserts for medications contain substantial information on adverse events (AEs) and their incidence as well as information on potential benefits. The physician also bears in mind that some side effects (or for that matter, some benefits) may not be recognized until years after the drug has become FDA approved.

Even in the case of older medications, however, evidence from meta-analyses and systematic reviews may also be lacking. In these situations, the physician's clinical experience is critical in order to relay to the patient some sense of the frequency and severity of adverse events as well as benefits. And yet the shortcoming of this process is that it is largely subjective. It is, in fact, acknowledgement of this subjectivity that has, in part, driven the development of EBP.

The subjective process of trying to determine if the benefits of a medication are worth the risks is akin to picking up two stones – one in each hand - and trying to decide which one is heavier. There is no measuring scale or recognized framework for relating the factors, benefit and risk, in even a semi-quantitative way. Even a balanced scale without numbers would be very useful in that it could determine with certainty which stone is heavier.

If this question of safety is posed to the FDA or to the pharmaceutical industry, a very different type of response will be forthcoming. For many years, the pharmaceutical industry and worldwide regulatory agencies, including the FDA, have been attempting to establish a widely accepted framework for assessing benefits and risks. After all, the FDA's mission statement is "FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation."[3]. Ensuring safety and efficacy is the heart and soul of the FDA. Safety and efficacy are also the two essential ingredients for a benefit-risk assessment.

If determining safety and efficacy are also the two primary goals of clinical research, why then isn't the data from clinical trials readily translatable into a usable benefit-risk assessment at the outset of a new drug's approval? The most crucial reason is that, despite enormous effort, there is no widely accepted, or "universal," framework for calculating and expressing this critical information. There are a number of proposed frameworks, including: a) the seven-step framework by the Centre for Innovation in Regulatory Science b) the eight-step PrOACT-URL by the European Medicines Agency c) the five-step benefit-risk framework by the US FDA d) the six-step BRAT framework by PhRMA e) the eight-step BRAIN framework by Novo Nordisk and f) the eight-step Universal Methodology for Benefit Risk Assessment.4 There is yet, however, no accepted framework in widespread use. In "Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit-Risk Balance of Medicines," Coplan states, "The current process of benefit-risk assessment of medicines relies primarily on intuitive expert judgement. Frameworks are needed for transparent, rational and defensible decision making that benefits patients, drug developers, and decision makers." [5]

Nearly all of the work in isolating and defining a universal framework has been undertaken by regulatory agencies and pharmaceutical companies. To be sure, these are convoluted conundrums, well-matched for an industry that has the resources for their resolution. Complex problems tend to beget complex answers. In Benefit-Risk Assessment of Medicines (2015), Leong, Salek, and Walker state that "It is therefore vital to establish a universal framework with the participation of major regulatory agencies to ensure the possible uptake of the same framework by other regulators across the world."[4]. Although it is reasonable that these two stakeholders, regulatory agencies and pharmaceutical companies, take the lead in forging a universal framework, it appears that it will take a number of years before benefit-risk assessments will be readily available for the majority of medications currently in use. What is needed now is a simple tool that can enable physicians and patients to make more rational decisions regarding drug therapy.

It is time to look at the problem from the perspective of the patient, the most important stakeholder. In Leong, Salek, and Walker's (2015) Benefit-Risk Assessment of Medicines, the authors write, "The regulation of medicines is essentially conducted to ensure patients' accessibility to medicines that fulfill the criteria of quality, safety, and efficacy. As patients are not equipped to make a scientific assessment, regulators play an important role in controlling the access to safe and effective medicines." [4]. Although the average patient may not be "equipped to make a scientific assessment," that patient is the very one who ultimately makes the decision as to whether or not to take a medication. And his decision is usually based upon some kind of subjective, benefit-risk assessment. Should a patient blindly adhere to a medication regimen based solely upon his personal physician's directive? In clinical research, subjects cannot execute an informed consent without adequate information about the investigational product. In clinical medicine, should not patients, armed with reliable benefit-risk information, also have the opportunity to make informed decisions? Perhaps, complex problems can find simpler, albeit temporary, solutions, at least until the complexities can be teased apart. Patients will continue to make decisions regarding the benefit-risk assessment of medications with or without directed assistance. An attempt should be made to, at least, provide a simple tool, a tool that ideally can be continuously honed and improved over time.

A benefit-risk analysis seeks to compare benefits and risks and may be expressed, in its simplest form, as a ratio. A ratio is, after all, the mathematical analog of a balancing scale.

The benefit-to-risk ratio can be thus formulated as an initial basic Equation #1:

$$\frac{\textit{Benefit}}{\textit{Risk}}$$

An example follows. A hypothetical arthritis medication works in 99 of 100 patients with only one reported adverse reaction (AR). The equation is refined:

$$\frac{\textit{Frequency of Benefit}}{\textit{Frequency of AR}}$$

Initially, the benefit-risk ratio looks acceptable – until it is disclosed that the adverse reaction was a death. Clearly, more than just the frequency of the adverse reaction must be considered.

Severity of the AR is a critical factor. The equation is modified as noted below.

$$\frac{\textit{Frequency of Benefit}}{\textit{Frequency of AR} \times \textit{Severity of AR}}$$

Another example follows with a different drug. With this drug, there is again a single adverse reaction out of 100 patients and that adverse reaction is again a death. But the drug was completely effective in the other 99 patients. Consider that all 99 patients had a diagnosis of terminal lung cancer and were, therefore, subsequently cured. So now the benefit-risk ratio looks incredibly good.

Clearly, not only the frequency of the benefit and the severity of the AR but also the severity of the underlying disease are necessary factors to consider. The equation is modified to include four specific variables.

$$\frac{\textit{Frequency of Benefit (Variable 3)} \times \textit{Disease Severity (Variable 4)}}{\textit{Frequency of AR (Variable 1)} \times \textit{Severity of the AR (Variable 2)}}$$

At first glance, this appears to be a simple, usable equation but considerable challenges remain. Although determining the frequency of adverse reactions is one of the major objectives of clinical research, that information is frequently not readily available. For instance, hydrochlorothiazide is known to cause hypokalemia but the exact frequency of that complication is not firmly established. Another question is how is "benefit" determined? And how is the severity of an adverse reaction graded? Furthermore, how Is the severity of a disease under treatment graded? Now the complexity of the problem begins to become clear.

Upon closer inspection, additional complexities can be appreciated. For example, the benefit of a drug may not be readily apparent. An example will help to clarify this odd statement.

Hypertension is treated because of its effect on accelerating vascular disease, primarily heart attack, renal disease, and stroke. Therefore, the benefits are secondary benefits and difficult to assess. Therefore, when the benefits of treating hypertension and the severity of this disease state are evaluated, the lowering of blood pressure is used as a surrogate marker for secondary phenomena.

The task of defining safety seems overwhelming, perhaps hopeless. Yet, there remains a desperate need to demonstrate in some readily understandable way, not only to patients but to the healthcare community in general, the benefit-risk ratio of drugs. What is needed is some initial, basic framework which can be refined over time as these variables become more certain and better understood.

In order for any equation to be valid, the variables must be clearly defined. For an equation to be useful, the values must be readily accessible. Therefore, simplicity will be a primary goal.

In the FDA's 21 CFR section 101.93(g) disease is defined as:

"...damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition."6 In this definition, the emphasis is on normal functioning.

For the purposes of this article, a drug will be defined as a substance "which has a physiological effect when ingested or otherwise introduced into the body."7 A medication will be defined as an FDA-approved drug that, when administered to a person, has a therapeutic effect.

The FDA defines an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."8 Therefore, an adverse event could be a symptom, an abnormal lab finding, a physical finding, or a clearly defined disorder or disease. If it should be determined that the adverse event is, in fact, caused by the drug, then the adverse event is termed an "adverse reaction." For the purpose of clarity, we will assume that causation is an association found to be statistically significant.

Equations also require assumptions. These assumptions will also be pointed out. The first assumption in considering the elucidation of the benefit-risk ratio is that the drug is being prescribed as outlined in the package insert. It would be impossible to determine risk if the medication is prescribed or taken in any way which it is prohibited. Interestingly, the restriction of medication to a particular subset of patients has become an effective strategy for maximizing benefits while minimizing risks.

Frequency of Adverse Reaction (Variable 1)

The frequency of adverse reactions is often contained within the package insert or may be found in systematic reviews. In those cases in which the frequency is not readily obtainable, the physician will assign his best guess estimate. Assigning a value based upon the physician's personal assessment is a weak area in this framework. But two things should be kept in mind.

The first is that the more serious that an AR is, the more likely that a frequency will be known and generally accepted. Secondly, as additional data become available, reliance on this type of estimate will decrease.

Benefit (Variable 3)

For the purpose of defining this variable, benefit will be understood to mean how well the drug does what it is purported to do. What drugs do can be broadly categorized in increasing order of importance as follows: 1) alleviates symptoms 2) ameliorates (or slows down) disease 3) halts disease progression 4) cures disease and 5) prevents disease. This classification is reflected in ideas set forth by the U.S. Department of Health and Human Services:

"A medication is a substance that is taken into or placed on the body that does one of the following things:

Most medications are used to cure a disease or condition. For example, antibiotics are given to cure an infection.

Medications are also given to treat a medical condition. For example, anti-depressants are given to treat depression.

Medications are also given to relieve symptoms of an illness. For example, pain relievers are given to reduce pain.

Vaccinations are given to prevent diseases. For example, the Flu Vaccine helps to prevent the person from complications of having the flu." [9]

From the DHHS classification, the treatment of a medical condition has been further divided into two subsets, medications that slow down disease and those that halt the progression of disease.

Therefore, the frequency of benefit is the frequency with which the drug achieves its primary goal.

Earlier in this paper it was pointed out that the difficulty in assessing the benefit-risk ratio of medications like anti-hypertensives and cholesterol-lowering medications stems from the fact that the benefits are secondary phenomena. If the prevention of cardiovascular disease is thought as the primary function, then the benefit-risk ratio is easier to conceptualize.

Severity of Adverse Reaction (Variable 2) & Severity of disease (Variable 4)

One of the biggest challenges in formulating a workable equation is in defining severity of AR and severity of disease. These terms must be defined such that they are "like-terms."

In an article entitled "Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement," the authors state:

Risk–benefit ratio: The most common expression for the comparison of harms and benefits. It is a technical term that assumes that a ratio can indeed be calculated. Because the benefits and harms of an intervention are often so different in character or are measured on different scales, the term "risk–benefit ratio" has no literal meaning. In addition, there may be several distinct benefits and harms. We advocate using "balance of benefits and harms" rather than "risk–benefit ratio." [10].

Clinical research provides some guidance here. The commonality of disease and adverse reaction is that they both affect health. Therefore, the challenge becomes to define both in terms of health. Health can be defined operationally as the "ability to function normally."

The severity of the adverse reaction can be operationally described in terms of its impact on a person's ability to function. Thus, ARs and diseases can be characterized by their effect on normal functioning, taken here to mean the ability to carry out activities of daily living. The concept of the effects on daily living is well established in clinical research.

Clinical research provides additional guidance. The National Cancer Institute published in May of 2009 the "Common Terminology Criteria for Adverse Events v4.0 (CTCAE)." CTCAE provides a grading system for all categories of AR, including symptoms, lab abnormalities, physical findings, and disease states. The grading system is described in the introduction of the document:

"Grades:

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

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

A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the

telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking

medications, and not bedridden." [11]

The CTCAE grading system will be used to grade both ARs as well as Disease Severity.

The next step in developing the equation is to define boundaries by assigning specific numerical weights to the variables. The benefit (Variable 3) is now further defined as "the frequency x the weight of the benefit."

$$\frac{\text{Frequency x Weight of Benefit (Variable 3) x Disease Severity (Variable 4)}}{\text{Frequency of AR (Variable 1) x Severity of the AR (Variable 2)}}$$

The best possible benefit-risk ratio is one in which the frequency of ARs and the severity of ARs both approach 0. As the risk approaches 0, the ratio increases. It is also apparent from this equation that when the benefit equals the risk, the ratio becomes 1.0. Therefore, any result greater than 1 would be favorable. Furthermore, the larger the number, the more favorable is the result. Mathematically, if the denominator was ever 0, then the equation would be unusable. Practically speaking, this is not a realistic concern since it is unlikely that any drug will ever be found to be completely devoid of ARs.

To assign some numerical weights to the various categories requires some further assumptions. The weights must be manipulated in such a way that a risk profile can be generated that is acceptable to the patient. Using this equation requires that in order to determine what constitutes an acceptable risk profile we must first determine what constitutes an acceptable risk. This will, of course, vary from individual to individual.

If people are queried about what would be an acceptable death rate for a medication that only manages symptoms of a "mild" disease, most respond that the risk of death would have to be zero. Many recoil even at the concept of "an acceptable death rate." When it is pointed out that even commercial airline flights carry some risk of death, albeit incredibly low (usually recognized at one in seven million), they will then modify their position that one in seven million would be acceptable. When it is pointed out that the risk of death in the setting of routine scheduled surgery is about 1 in 100,000, many would then reconsider and deem a risk of 1 in 100,000 as being acceptable. This assumption will be used to assign weights for both benefit and severity of disease. The weight for death as an AR will be, of course, assigned the highest weight of 1. In this case, the assumption is the drug is 100% effective. The severity of disease under treatment is assumed to be mild.

$$\frac{\text{Frequency x Weight of Benefit x Severity of Disease}}{\text{Frequency of AR (1 in 100,000) x Severity of AR (1)}}$$

$$\frac{\text{100\% x alleviates symptoms x Severity of Disease}}{\text{0.00001 x 1}} = 1$$

In order to set the lower limit for this equation (i.e. where the benefit equals the risk), the least beneficial category of medication, i.e. alleviates symptoms, has been chosen. The disease with the lowest severity (mild) has also been chosen. One additional assumption will be that the weight of the benefit will parallel the weight for the severity of disease. The weights for "alleviates symptoms" and severity of disease must be assigned such that their multiplication approaches the number, 0.00001. The square root of 0.00001 is approximately 0.00316.

Using these limits, I have extrapolated the weights for the other variables.

Severity of ARs and Severity of Disease:

- Mild - 0.0032
- Moderate - 0.25
- Severe - 0.75
- Life threatening – 0.9
- Death – 1.0

Weight of Benefit:

- Alleviates symptoms – 0.0032
- Slows disease – 0.25
- Controls disease – 0.75
- Cures disease – 0.9
- Prevents disease – 1.0

There is subjectivity in how the weights for grades 2 through 4 were assigned for severity of AR, severity of disease, and benefit. In the future, weights could be assigned by a consensus of opinion leaders. These weights could also be assigned in such a way to account for the patient's own preferences.

Examples follow. Any value > 1.0 will be seen as a positive benefit-risk ratio for the proposed treatment.

An antibiotic which has, as its most common AR, diarrhea, is being used to treat pneumonia. This AR occurs in 10% of patients and that its severity is generally moderate (i.e. a weight of 0.25). We will further say that the antibiotic cures pneumonia in about 90%. The pneumonia is graded as severe.

$$\frac{\text{Frequency x Weight of Benefit x Severity of Disease}}{\text{Frequency of AR x Severity of AR}}$$

$$\frac{(0.9) \text{ x } (0.9) \text{ x } 0.75}{0.1 \text{ x } 0.25} = 24.3$$

A result of 24.3 is clearly favorable.

Alter the above equation as follows. The adverse reaction is colitis due to *clostridium difficile* with an occurrence rate of 30% with a severity of severe. The numerator will be the same.

$$\frac{0.9) \text{ x } (0.9) \text{ x } 0.75}{0.3 \text{ x } 0.75} = 2.7$$

Alter the variables once more. Instead of pneumonia, the disease will be pharyngitis with a designated severity of 0.0032. Now the benefit-risk ratio becomes 0.012 clearly an unacceptable treatment option.

With the vast majority of FDA-approved drugs, there are generally multiple ARs that are recognized. In this situation, the frequency and severity for each AR is calculated and added to the denominator. As long as the ratios is greater than 1, then the overall benefit-risk assessment would be favorable.

The drug may actually cause a well-recognized disorder or disease which may be manifested by multiple symptoms, physical findings, and lab abnormalities. Again, clinical research provides insight. When evaluating AEs, the principal investigator reports symptoms and laboratory abnormalities as isolated findings only if there is no encompassing diagnosis. Therefore, in this instance, the only AR to be calculated would be that which is related to the encompassing disease.

Admittedly, there are challenges that would have to be dealt with before this approach could be fully implemented.

As an example, consider a hypothetical disease that is uniformly fatal unless a newly discovered medication is administered. This new medication cures the disease in 50% of patients. However, the 50% who are not cured succumb to fatal cardiotoxicity.

$$\frac{\text{Frequency x Weight of Benefit (Variable 3) x Disease Severity (Variable 4)}}{\text{Frequency of AR (Variable 1) x Severity of AR (Variable 2)}}$$

Benefit = 50% (Frequency of Benefit) x 0.9 (the Weight for cure)

Disease severity = 1 (the Weight for death)

Frequency of AR = 50%

Severity of AR = 1

These values yield the equation below:

$$(0.5 \text{ x } 0.9 \text{ x } 1.0)/ (0.5 \text{ x } 1.0) = 0.9$$

A value of 0.9 signifies an unfavorable result. Most patients, however, would view this drug as having a very acceptable benefit-risk assessment, i.e. a 50% chance at survival. One potential solution would be to increase the weight of cure to some value > 1.

There well may be other situations that demonstrate flaws in this approach.

What this approach does not attempt to address is how the information on frequency of ARs is collected. Much of that data is obtained from post-marketing surveillance. It is, however, beyond the scope of this paper to address the complexities of compiling this data.

Pharmaceutical innovation also poses another impending challenge. Drugs are currently being studied as a means of ameliorating the effects of aging which has yet to be defined as a pathological process. For example, there are a number of compounds under development for age-associated memory impairment. Therefore, we may soon have a new class of compounds that enhance well-being, as opposed to treating or preventing disease. New definitions for disease and medication may be needed.

It is arguable that such "medications" have already been approved. Medications for sleep deprivation and for some cosmetic conditions are two examples. Such a class of medication poses significant questions with regard to the benefit-risk assessment because there is no disease process that is being addressed. Although such novel medications do not appear to fit into universal frameworks that have been already mentioned, this proposed benefit-risk ratio could be adapted by simply removing Variable 4 from the equation and appropriately adjusting the weight of the benefit variable.

This paper is not advanced as a final blueprint for the complete assessment of risk and benefit but strives to show how insights from clinical research may help in approaching the problem from a different perspective.

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