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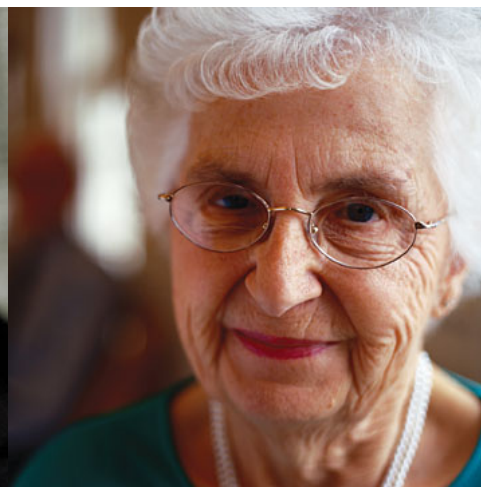
*Your health and
safety... our priority.*

*Votre santé et votre
sécurité... notre priorité.*

A Regulatory Approach to Uncertainty for the “Real World”

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**Characterizing and Communicating Uncertainty in the
Assessment of Benefits and Risks of Pharmaceutical
Products: An IOM Workshop**
May 12, 2014, FDA Campus, White Oak, Maryland



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Recall from IOM Uncertainty Workshop Day 1

B. Fischhoff:

- a core aim of the workshop: how to make uncertainty “**cognitively tractable**”

So Let's Consider Some Basics about Uncertainty and Cognitive Traction

Note:
Confusion is a
synonym for
uncertainty



Hypothesis 1:
Cognitive traction is
hindered by
confusion

Thesaurus.com

uncertainty [see definition of uncertainty](#)

noun doubt, changeableness

ambiguity	trouble	doubtfulness	misgiving
ambivalence	uneasiness	dubiety	mystification
anxiety	unpredictability	guesswork	oscillation
concern	worry	hesitancy	perplexity
confusion	bewilderment	hesitation	puzzle
distrust	conjecture	incertitude	puzzlement
mistrust	contingency	inconclusiveness	qualm
skepticism	dilemma	indecision	quandary
suspicion	disquiet	irresolution	query
reserve			
scruple			
vagueness			
wonder			
lack of confidence			
questionableness			

Hypothesis 2: “Benefit–Risk” is Inherently Confusing

Reason # 1:

There is asymmetrical acknowledgement of uncertainty in the terms:

- “benefit” does not include concept of uncertainty;

benefit synonyms:

**good
advantage**



- “risk” includes, and can even substitute for, “uncertainty”.

risk synonyms:

**chance
uncertainty**



Hypothesis 2: “Benefit–Risk” is Inherently Confusing

Reason # 2:

“Risk” has wide ranging and “slippery” definitions.

Synonyms of *risk* in English:

risk  Oxford Dictionaries
Language matters

NOUN

1 *‘to publish the story was indeed a risk’ ‘the certain amount of risk involved’*

[ANTONYMS] safety

chance, uncertainty, unpredictability, precariousness, instability, insecurity, perilousness, riskiness, gamble, venture

risk  *noun* \ˈrisk\

: the possibility that something bad or unpleasant (an injury or a loss) will happen

: someone or something that may cause something bad or unpleasant to happen

: a person or thing that someone judges to be a good or bad choice for insurance, a loan, etc.

haz·ard  *noun* \ˈhɑ-zɑrd\

: a source of danger

golf : something on a golf course (a patch of sand) that makes hitting the ball difficult

Full Definition of HAZARD

1 : a game of chance like craps

2 : a source of danger

3 a : **CHANCE, RISK**

b : a chance event : ACCIDENT

4 *obsolete* : STAKE 3a

5 : a golf-course obstacle

— **at hazard**

: at stake

Synonyms of *hazard* in English:

hazard

NOUN

1 *‘the hazards of high-energy radiation’*
danger, risk, peril, threat, menace; difficulty, problem, pitfall; jeopardy, perilousness, endangerment, imperilment

2 *‘we can form no calculation concerning the laws of hazard’*

chance, probability, fortuity, luck, fate, destiny, fortune, providence, serendipity, accident; *North American* happenstance

Hypothesis 2: “Benefit–Risk” is Inherently Confusing

Reason # 3:



“Because of its multiple meanings, “risk” conflates considerations of the tolerances and the trade-offs.

NB:

tolerance for risk $\neq$ **tolerance for uncertainties**



“possibility of harm”



“about harms, benefits, other..”

Hypothesis 3:

“Benefit – Harm – Uncertainty” is Less Confusing

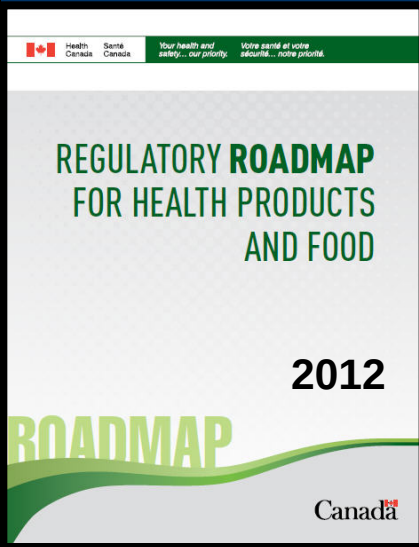


This trio of distinct and unambiguous terms may be helpful in considerations of:

- **positive treatment effects**
 - **negative treatment effects**
 - **uncertainties in +/- effects, and other issues (e.g. situational)**
 - **tolerances:**
 - known, potential negative effects
 - positive effects' uncertainties
- clarifying trade-offs.

**Increased
cognitive traction?
We think so.**

HC'S New Regulatory Approach



“BHU”

“Benefit-Harm-Uncertainty” Management

- this approach will be applied across products and product lifecycle
- there will also be mandated transparency about our “BHU” considerations
- system will be designed to align regulatory information and communications for easier consideration by health partners...including patients

**“hard-wired” into
the Regulations**

(David K Lee et al, OLRM, HC)

Recall Also the Problem Statement from IOM Uncertainty Workshop Day 1

T. McDaniels:

- “eliciting values for risk management choices involves application of structured...common sense to complex problems.”
 - entails the combination of...information and judgements, to clarify and examine trade-offs.
 - process should be explicit and transparent”

HC's Solution:

A structured, common-sense approach to uncertainty management & communication for the “real-world”

First, design the information system from the patients' end; then, work “backwards”

User-friendly, on-line guide is in the works

cognitively tractable
(at least for some)



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PATIENT'S DECISION GUIDE ABOUT TREATMENTS

A structured and step-wise process to help you to think through positive effects, negative effects and uncertainties of treatments

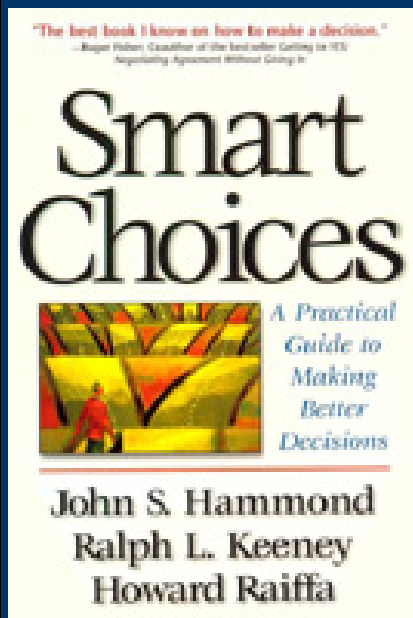
so you can make best informed treatment decisions for yourself



Developed in partnership between
Health Canada and patients

Our Starting Point for the HC Patient's Decision Guide

We reworked this book's "Keys to Effective Decision Making"



1. Objectives “Goals”
2. Cognitive Traps “Discovering my thinking”
3. Problem “Opportunities”
4. Alternatives
5. Evidence
6. Uncertainties
7. Linked Decisions “Anticipating other decisions”
8. Consequences “Imagining outcomes”
9. Risk and Uncertainty Tolerances
10. Trade-Offs “Considering the trade-offs I am willing to make and those I am not”

John S. Hammond, Ralph S. Keeney, Howard Raiffa. *Smart Choices. A Practical Guide to Making Better Decisions.* 1999. Harvard Business School Press. Boston, Mass.

Highlights of the Patient's Decision Guide

ABOUT THIS GUIDE

Welcome to our Patient's Decision Guide about Treatments!

Health Canada has developed this Guide in collaboration with patients who are very experienced with their diseases/conditions, the treatments and their healthcare system so that you can gain from their insights as you consider your own circumstances and choices.



This Guide is structured, with decision science approaches in mind (see reference 1 in Appendix 4), so that you can also benefit from a step-wise and measured "walk" through your thinking and judgements, starting with your personal values right the way through to imagining how the outcome of your possible treatment choices might feel to you. This way, you will be less likely to "jump" to conclusions and decisions. You will also be more likely to ask clear and focussed questions of others, such as your healthcare team, and therefore receive answers that will be of most help to you as you make your decisions.



In addition, you will find lots of candid information in the Guide on how treatment products are developed and regulated and what you can expect, in general, about products you may use. You may already be aware that, really, there are few treatments that are simple "magic bullets" but we hope that the Guide can help you get a clearer picture of things, no matter how experienced a patient you may be.

In the end, if you can think as clearly as possible about your situation and disease/condition AND be well informed and practical about the effects of - and the remaining uncertainties about - your treatment options, you will increase your chances to make choices that are best for you and to feel in control of your medical treatment issues.

helpful images



STEP 1: SETTING MY GOALS

patients' stories

In this opening section, you will be thinking about what really matters most to you about your health situation. Being clear about this at the outset will help set a well-defined course for the rest of your journey through your issues and options.

What is/are my main objectives, or goals, with respect to my disease/condition?

FOR EXAMPLE:

- I want to:
- live as long as I can
 - live with as good quality of life as possible and "feel better"
 - be able to return to work
 - be more independent in my daily activities

"All patients hope that what their doctor has prescribed will help them return to their previous life, before they received their diagnosis."

"I think that one of the first thoughts that goes through anyone's mind when they heard the words 'you have cancer' is: can you cure me? A cure is of course ideal, but in the absence of a cure, 'stable disease' (in other words, cancer that is temporarily not growing) is an excellent outcome. In my case, it has helped me to focus on the present: when I have stable disease, I often remind myself 'I don't know what tomorrow will bring, but today, I can do anything that I would have done if I didn't have cancer.'"

Can I think of other goals that are important to me?

If I had to choose, which is my most important goal? Why? Can I list the rest of my main goals in descending order of importance to me?

Contributions from Actual Patients

"I have thought about the possibility of enrolling in clinical trials of experimental treatments for my disease and have decided that I am not yet at a life stage where I would feel able to deal with the higher uncertainties about the positive and negative effects, compared to licensed treatments. I am still working full time while living with my chronic disease and need to be able to assure myself that I will not have to unexpectedly take time off sick from work to recover from an unpredictable negative treatment reaction I might experience."

"I know I have to make some decisions about my treatment. How do I do this when no one in my family wants to have a real conversation about this? Everybody is trying to protect everybody. With the help of the medical team we were finally able to have an open conversation about what we were each scared of. Once we could do that I was able to come up with a treatment plan that worked for me and my family. While the worry will never completely go away it helps that we all know what to expect with this treatment plan."

**Some patients' stories
about uncertainty, fear**

STEP 2: DISCOVERING MY THINKING



(or)



This section encourages self-reflection and recognition of personal psychological, cognitive traps

[Portrait of Jeanne Hébuterne, profile, Amadeo Modigliani, visipix.com]

[Swan looking at its reflection in still water]

It's time now to think about who you are and what makes you tick: why you think and decide the way you do, in general. Investigating this may help you understand more clearly the motivations behind your reactions and judgements, which in turn may help you to be at your clearest in your mind when you come to make treatment decisions.

- Am I in a situation which may influence my ability or willingness to think things through at the moment?
- Can I recognize specific aspects of my situation, or about myself, which may influence, or even skew my thinking? Are these influences actually reasonable and meaningful to me?

Questions the Patient Could Ask are Included Throughout the Guide

FOR EXAMPLE: For each treatment option, consider:

Positive Effects:



[Two hands showing thumbs up against a blue sky]

Some of the questions about treatment benefits

These often anticipate uncertainty considerations

- What are the known potential benefits of the treatment for my disease/condition? E.g.:
 - Does it alter disease progression or provide symptomatic management?
 - How much benefit, and what kinds of benefit, are expected?
 - How many of the patients with the disease are expected to achieve benefit?
 - How long does it take before benefit is felt?
 - How long does treatment benefit last, if I take the treatment as recommended?

Negative Effects:



[person about to write out a list of advantages and disadvantages in a side-by-side list on paper]

Some of the questions about negative effects, separated, for clarity, into serious and less serious effects

How safe is each of the treatment options for me? Specifically:

- i) For each treatment option, can the serious treatment toxicities (i.e. potentially irreversible, life-threatening) be managed (i.e. reduce the potential for occurrence, reduce the severity) in my particular circumstances?
- ii) For each treatment option, can the troublesome, or minor negative effects of the treatment (i.e. unpleasant, inconvenient but not serious effects) be managed in my particular circumstances?

**There is a
whole section
on
uncertainties**

**Introductory
text guides
the patient
through the
thinking**



STEP 6: EXPLORING THE UNCERTAINTIES FOR EACH OF MY TREATMENT OPTIONS

Well done! If you have reached this step, you have a good grasp of what is known about your treatment options and their anticipated performance.

Now we will turn to a hazier but very important issue: what is not yet known. In fact, in your investigations through Step 5, you might have already seen this issue crop up, for example, about whether it is known if patients like you are likely experience the positive effects and/or the negative ones.



[Outline of mountains partially hidden behind mist]

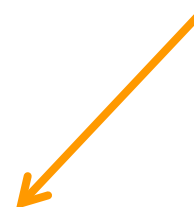
Life holds uncertainties. This is no less true in the world of medical treatments, in large part because of the many complexities of the science and how to interpret the evidence, patient's individual situations and physical characteristics responses to treatments and their particular choices which affect how they are affected by treatments. These uncertainties have always existed but regulators are now making efforts to do better at letting the public know about them, so that they do not have false expectations.

In this section, you are encouraged to explore "what we know we don't know". That is, what the remaining uncertainties about positive and negative effects of treatment may be - and to do so while thinking about your particular situation and needs. For many of these questions, you may want to ask your healthcare team or a disease support/advocacy group for their thoughts and/or to point you to where to get this information.



[Ancient Sound Abstract on Black, 1925, Paul Klee, WMOFA.com]

questions about uncertainties



What is still not clearly understood after licensing about the potential benefits and harms of the treatment?

Have any issues come up in the real-world, since the treatment was licensed, that relate to the positive and/or negative effects on patients? How uncertain is the on-market evidence and therefore how uncertain are the experts in their judgements about these issues?

Are the various conclusions in the evidence and information that I have considered consistent with each other about the potential benefits and harms of the treatment? Do the experts and those on my health care team agree with each other's conclusions?

Has the experts' understanding of the treatment's potential benefits and harms changed recently? If so, why?



[tall grasses blowing in the wind]

"I love my doctor. She is so conscientious and is always very honest with me about what is known about possible treatments and what is not known. She is never afraid to admit uncertainty – even her own. That is one of the reasons that I respect and trust her so much."

**more questions
about uncertainties**

Which of the uncertainties is/are of most importance or concern to me?

If there are uncertainties about the treatment's potential benefits and harms, how are these being handled by the experts?

For example, are there patient registries and/or further studies to be conducted? Why are these studies being performed? Have these been required by the government regulator? If so, could/should I join any of these?

“True / False / Maybe” quiz on uncertainty

TRUE, FALSE or MAYBE?

- 1) The information is complete about a treatment's potential benefits and harms at time of licensing.
- 2) Treatments are not usually studied, before they are licensed, under real-world conditions, with real-world patients like me.
- 3) It is not easy yet to collect reliable information on a treatment's potential benefits and harms once it is on the market.
- 4) There can be differences of opinion amongst the experts about the potential positive and negative effects of a treatment, both before and after it is licensed.
- 5) It is clear what the most effective dose is for individual patients like me, in order to give me the best chance of experiencing the treatment's benefits while minimizing the negative effects.
- 6) The best practice of science results in certain answers and fully-understood “truth”.

The Tolerances and Trade-Offs Section

STEP 10:

IDENTIFYING TRADE-OFFS I AM WILLING TO MAKE AND THOSE I AM NOT



[Several seesaws in a playground tipping in different directions]

Just as life is full of uncertainties, it is also a reality that it is often not possible to “have your cake and eat it too”. Making trade-offs is a basic part of many of our decisions every day. When we decide to save rather than spend, we have successfully convinced ourselves that the long-term security benefits of having money in the bank for a rainy day outweigh the ego-pleasing, short-term benefits of collecting expensive objects or experiences. Similarly, when we decide to refrain from having that piece of cake, we have realised that the longer term health benefits of keeping our blood sugar levels and calories in check outweigh the immediate sensory benefits to our taste buds.

In this case, here’s what it comes down to: you have a burden because of your disease that you want to reduce. But many, if not all, treatments come with the potential for both negative as well as positive effects and therefore a treatment may make your burden heavier in some ways (from the side effects that you might experience). On the other hand, the treatment may reduce your burden in other ways (from the positive effects on your disease that you might realise). The key question is: which treatment, or combination of treatments, has the most acceptable possible negative effects to you, given its potential for giving you positive effects? Put another way: which treatment(s) give(s) you, as far as you can tell, a best chance to reduce your overall health burden?

talks the
patient
through some
tricky thinking

general questions about tolerances and trade-offs

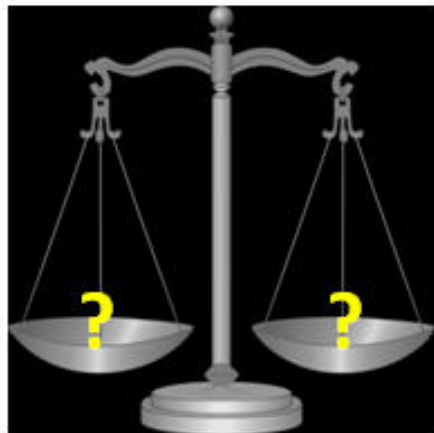
You might want to ask yourself:

In order to get the potential benefit from taking the treatment, what trade-offs of potential harms and/or uncertainties do I need to make?

What is my tolerance for the potential negative effects of treatment: my “risk tolerance”? In other words, how much potential harm(s) from negative effects of the treatment am I willing to endure, if I could get treatment benefits?

What are my tolerances of different aspects of my disease/condition? If I had to make a choice, would I be willing to treat the aspects that are most important to me first, or most?

Benefit-Harm Trade-Offs under Uncertainty:



"When I was diagnosed with HIV only one drug was available. I was told it could prolong my life for up to two years. At first I took it, believing that I wanted to live more than anything. After two months of experiencing much fatigue that I couldn't do anything, I stopped taking the drug. I told my doctor I would rather live two years with good quality of life than four years of misery."

[Old-fashioned weigh scale with yellow question marks over each of the weighing bowls]

How comfortable would I feel to take this treatment, if the experts are unsure about (or do not agree on) if, or how well, it works and how safe it is?

Would I rather wait to take this treatment when doctors understand more about if, or how well it works and how safe it is?

Does the seriousness or severity of my disease or condition, or the urgency needed to manage my disease or condition, affect my tolerance for uncertainties with the treatments?

How much uncertainty, and what kinds of uncertainties, about the potential positive and negative effects of the treatments, am I willing to risk in order to try to treat my disease/condition/disability?

Do my feelings about my disease/condition affect my uncertainty tolerances? How much of a benefit is it to me to be able to try something, even if its effects are still unclear? Have I thought seriously about how I feel about this?

Do the feelings about my disease/condition/disability that others that I care about have affect my tolerance of uncertainties?

specific questions about benefit-harm trade-offs under uncertainty

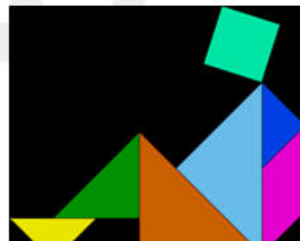
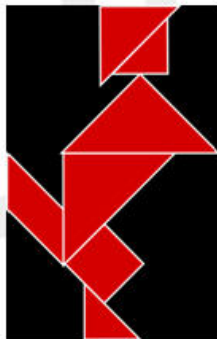
STEP 11:

RATING MY TREATMENT OPTIONS BASED ON THEIR ULTIMATE VALUE TO ME

At last! It is time to put everything together and apply the suggested guiding principles for making good decisions from Step 3 to the knowledge you now have on each of your treatment options.

It is possible, though, that you will not be able to come up with a clear order, or ranking, for your options. In fact, they may be so different that it may feel like you will be choosing between apples and oranges. That is perfectly fine, too. In any case, "sleeping on it" may give you clearer answers in the morning.

Again, talking with others is often very helpful to one's thinking. Please be aware, however, that while one option may rate best for one person, it may not be the best for someone else and so do not be surprised if you find differences of opinion!



[Two sets of tangrams, each displaying different versions of

From what I now know about each of my treatment options, AND how I feel about their positive and negative features AND how I feel about the trade-offs I am willing, or not willing, to make:

- which treatment(s) may best achieve my particular health goals?
- which treatment(s) do I have most confidence in? Why?
- which treatment(s) best suits my own values and circumstances? Why?
- which treatment(s) do I have least confidence in? Why?
- which treatment(s) least suits my own goals, values and circumstances? Why?

putting it all together:
valuing each treatment
as a whole, based on
the patient's particular
situation

PARTING THOUGHTS

- “Can we get people to embrace uncertainty without fear or scepticism?”
- We should try and quantify our uncertainty where possible.
- But also need clear language to honestly communicate deeper uncertainties, with due humility and without fear.”

David Spiegelhalter

**Winton Professor of the Public Understanding of Risk
University of Cambridge**

from: Quantifying and Visualising Uncertainty

<http://www.mth.kcl.ac.uk/finmath/semfiles/DS.pdf>