Start thinking HTA early

15/07/22; Anja Schiel, PhD, Special Adviser / Lead Methodologist in Regulatory and Pharmacoeconomic Statistics; Scientific Advice Working Party member; Methodology Working Party member; Vice-Chair EUnetHTA21 JSC CSCQ

Norwegian Medicines Agency

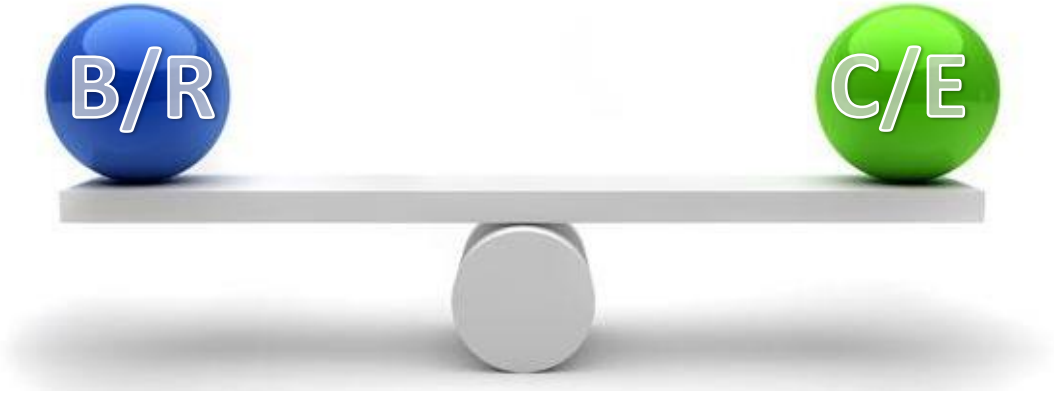
Disclaimer

The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the Norwegian Medicines Agency (NoMA) or of the European Medicines Agency (EMA) or its scientific committees or reflecting the position of the EMA.

Why is what is good enough for approval not good enough for reimbursement?

The difference

- Health economic models predict the future based on available data from different sources



- All models are wrong; some models are useful

George E. P. Box; Norman R. Draper (1987)

The underlying questions differ

- Clinical trial = Regulator

Efficacy (B/R)

Does it work in experimental setting

Population selected

Placebo or a selected comparator

- Real world = HTA

Effectiveness (C/E)

How does it work in medical practice

Patients as they come

Many alternative treatments

Type	Unit of effect	Strength	Limitations
Cost–benefit analysis (CBA)	All effects measured in €	The net benefit (NB) is easy to interpret. When a new treatments extra benefits are worth more than the extra costs then NB > 0	• It is difficult to measure the value of all health outcomes (positive or negative) in € • Ethical aspects come into the discussion (Prioritisation, discrimination, the Pareto principle)
Cost-utility analysis (CUA)	Two effects (quality and length of life); reflected as quality-adjusted life years (QALY's)	Patient relevant outcomes involving both quality and length of life can be incorporated into the analysis. In theory the QALY measure is 'universal', allowing evaluation of very different decision problems with each other.	• QALY outcomes can be biased by method, indication and population • Society might value a QALY for different patient groups differently (and who should we ask, patients or healthy people form the street?)
Cost-effectiveness (CEA)	Effect measured in 'natural units'	There is one outcome and it is measured in it's 'natural unit'.	• Only one outcome is considered for the effect conclusion (no context)
Cost-minimization (CMA)	No effects measured	Only cost data are needed	• Few treatments have truly identical outcomes • Still some evidence is needed to confirm the assumption of 'equality'

Modified from: Hoch JS, Dewa CS. An Introduction to Economic Evaluation: What's in a Name? *The Canadian Journal of Psychiatry*. 2005;50(3):159-166.

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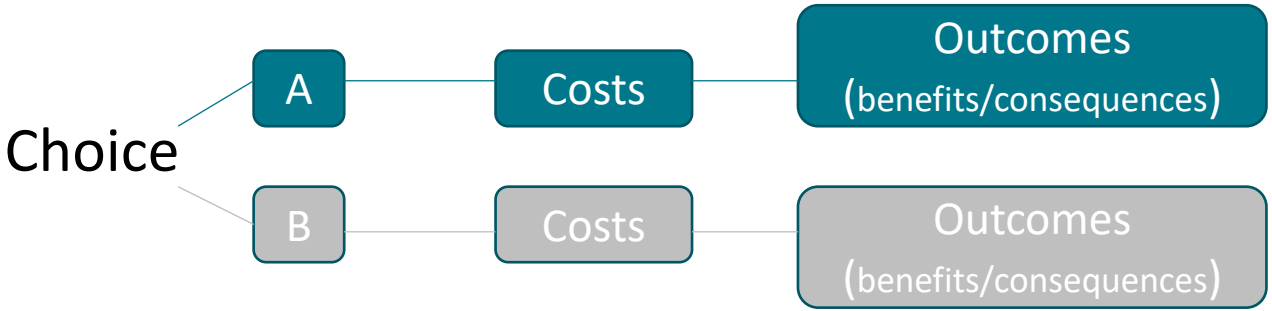
HTA: the basics

- The aim is to **maximize the health of the total population within the given budget**
- HTAs want value for money!



$$\text{ICER} = \frac{\text{Incremental costs (A-B)}}{\text{Incremental benefit (A-B)}}$$

Economic evaluation
'the **comparative analysis** of alternative courses of action in terms of both their **costs** and **consequences**'
(Drummond McGuire, 2001)

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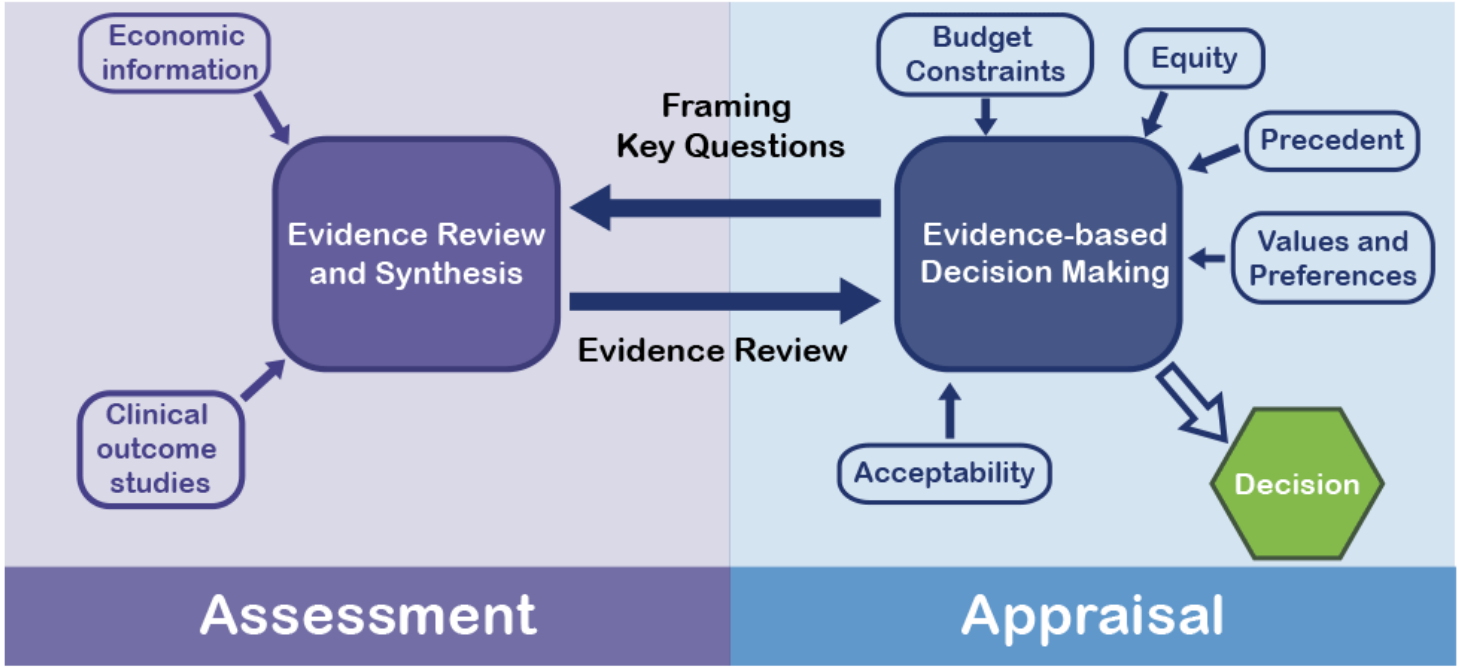
The two main components of HTA: Assessment and Appraisal



EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Adapted from Teutsch, S., Berger, M. (2005). 'Evidence synthesis and evidence-based decision making; Related but distinct processes. *Medical Decision Making,* pp. 487-489.

Choose your perspective

Societal perspective

- Medical costs borne by third-party payers and paid out-of-pocket by patients
- Time costs of patients in seeking and receiving care
- Time costs of informal (unpaid) caregivers
- Transportation costs
- Effects on future productivity and consumption
- Other costs and effects outside the health care sector

Health sector perspective

- Include all costs and benefits impacting a system of providers, payers and patients.
- Do not consider impact outside of the health system (e.g. long-term value to patients)
- Based on Direct Medical Costs reimbursed by a third party
- Can include out-of-pocket costs to the patient
- Can include current and future costs as a result of a pathway of care

Patient perspective

- Fees for consultation
- Bed day charges at the health facility
- Expenses on medicines, diagnostic tests,
- Travelling expenses to the health facility for the patient and accompanied persons for treatment,
- Amount spent on meal / food taken while waiting for treatment
- Time loss of the patient and the accompanied persons for seeking treatment
- Informal caregiving
- Pain and suffering

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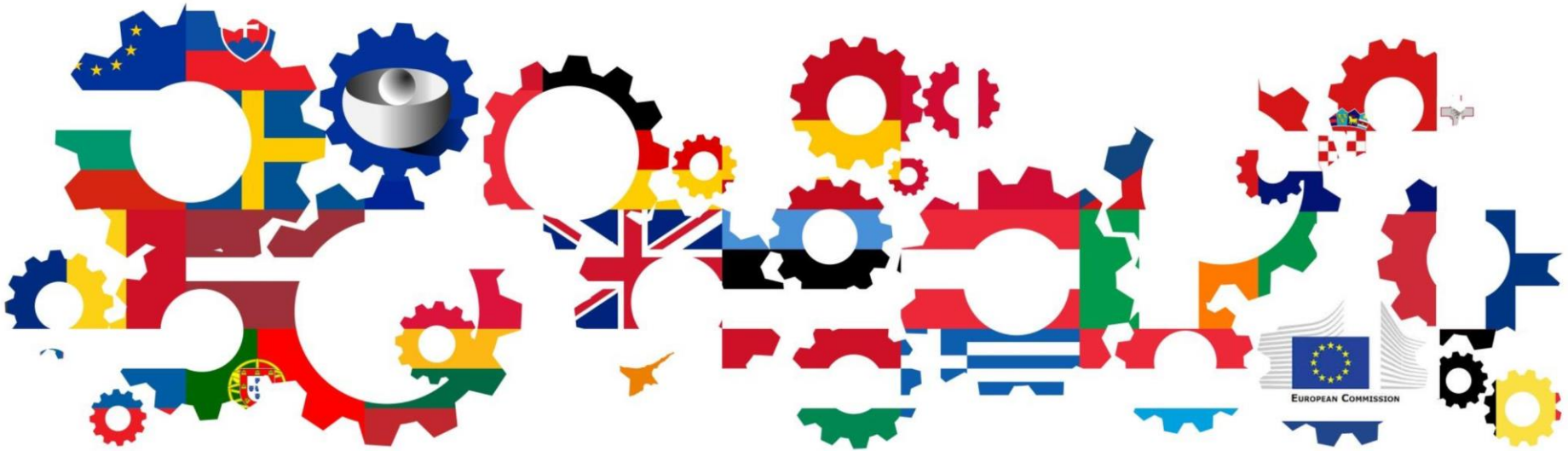
How do you want it - the crystal mumbo jumbo
or statistical probability?

The European medicines regulatory network



~ 50 national regulatory authorities | European Commission | European Medicines Agency

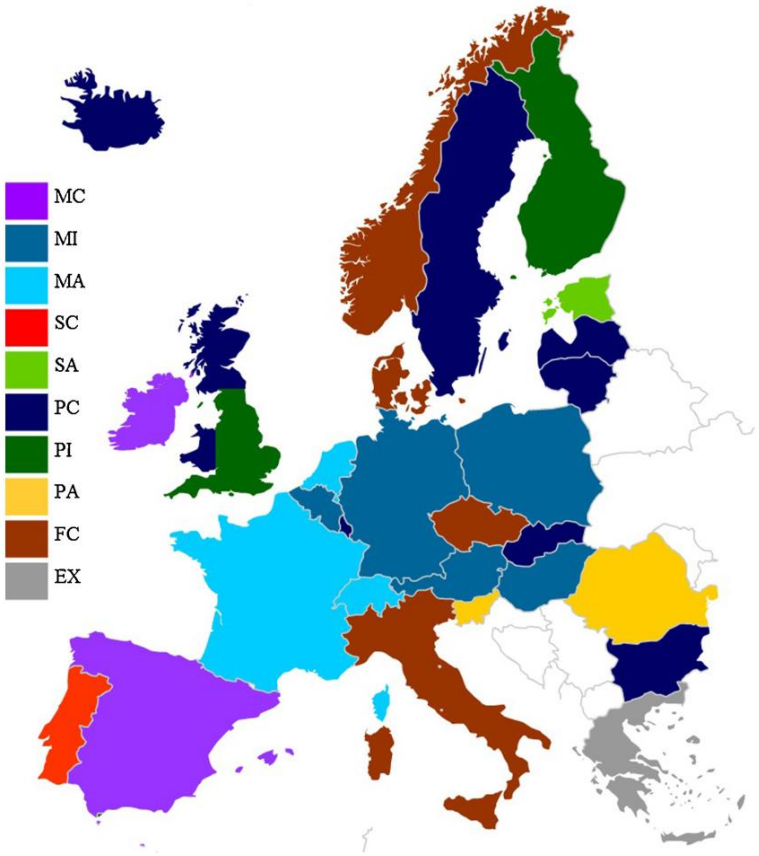
How to do things differently (for a reaon)…..

Cost-effectiveness

Added clinical Benefit

Budget optimisation

…and highly complicated



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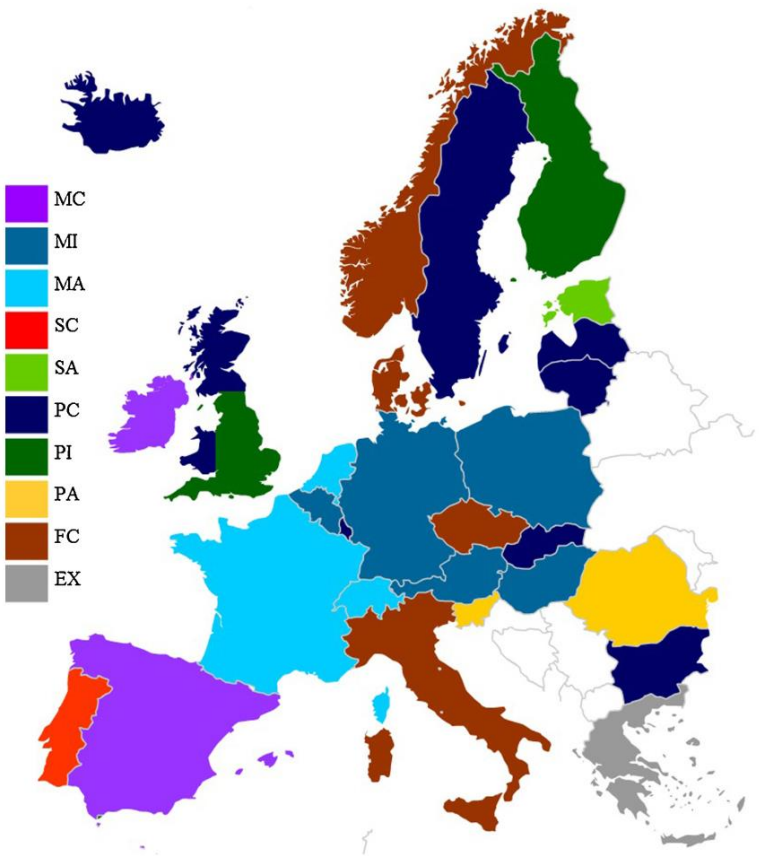

Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems

Nicola Allen[a,b,*], Franz Pichler[b,c,1], Tina Wang[b], Sundip Patel[a], Sam Salek[a]

[a] Centre for Socioeconomic Research, School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, UK
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[c] Eli Lilly and Company, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK

System Process Archetypes

HTA Process Archetypes

	M	S	P	F	E
C	DC (CYP) NCPE (IRE) DGFPS (SPA) MOH DTC (MAL)	INFARMED (POR)	AWMG (WAL) PDL (BUL) IMPRC (ICE) CHE (LAT) LRC (LIT) MSS (LUX) CC (SVK) SMC (SCO) TLV (SWE)	SUKL (CZE) DKMA (DEN) NOMA (NOR) AIFA (ITA)	
I	HEK (AUS) INAMI (BEL) IQWIG (GER) OHTA (HUN) AHTApol (POL)		NICE (ENG) HILA (FIN)		
A	HAS (FRA) CFH (NET) FDC (SWZ)	SAM (EST)	MoH (ROM) ZZZS (SVN)		
X					GREECE LIECHTENSTEIN

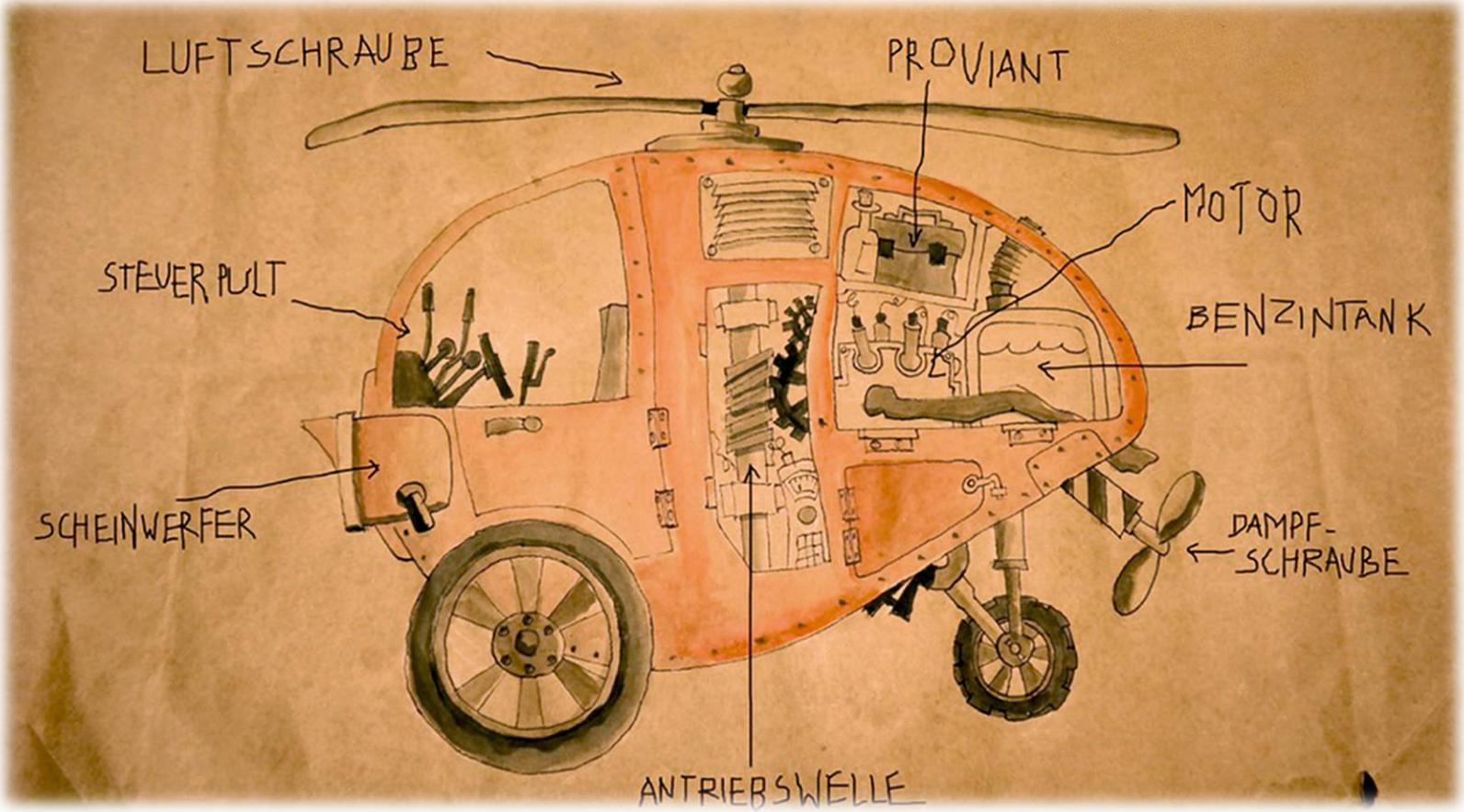
Archetype Key: MC, MI, MA, SC, SA, PC, PI, PA, FC, EX

Now lets go on a tour with worlds most impressive invention as an example…

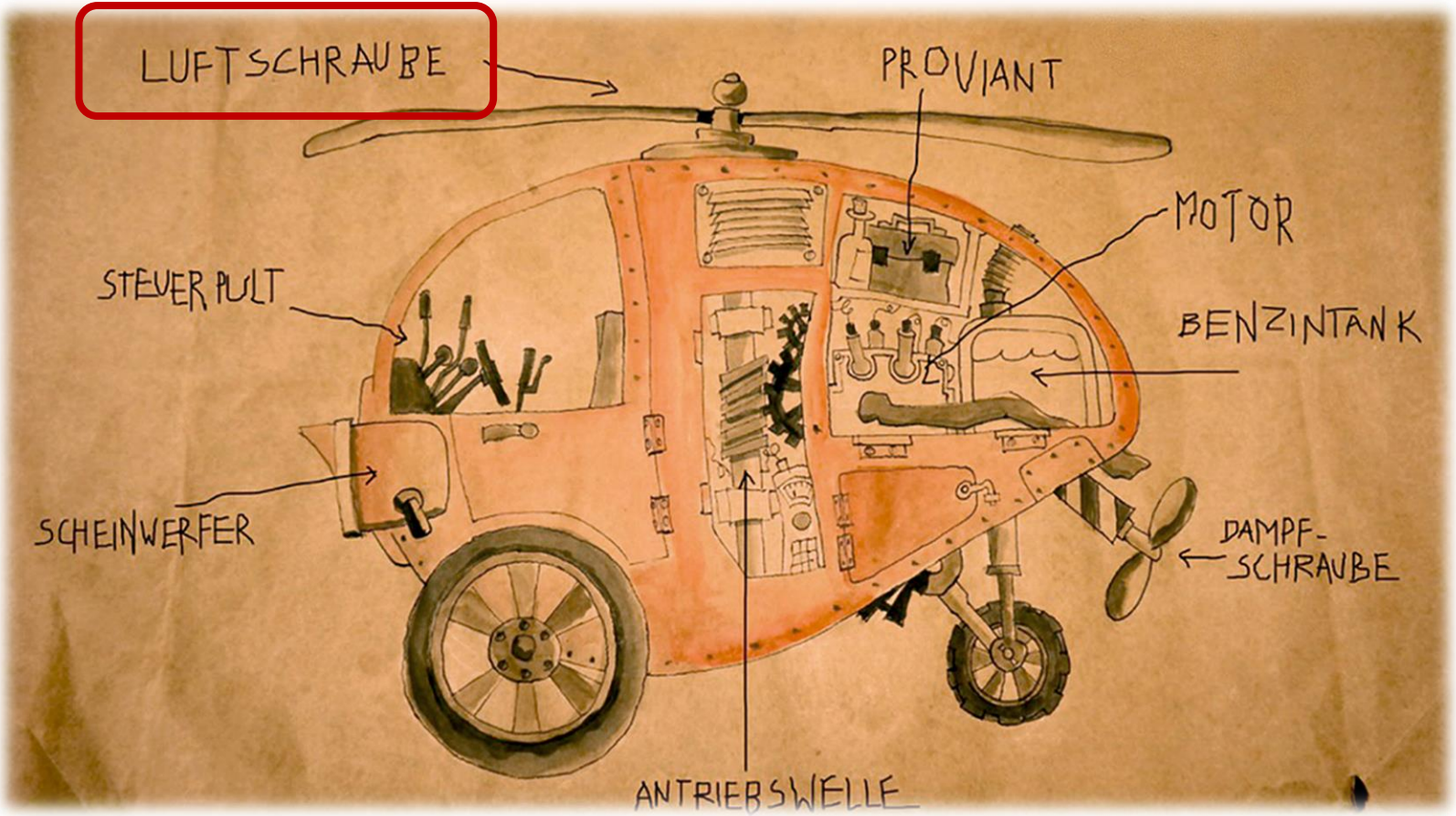
To get you out of the drug-development corner

- My example will be the world famous Fliewatüüt
- Based on the development of this ground-breaking new vehicle I will explain how the assessment of the B/R would likely be conducted and what the challenges might be to get it reimbursed.
- Let’s meet the contender……

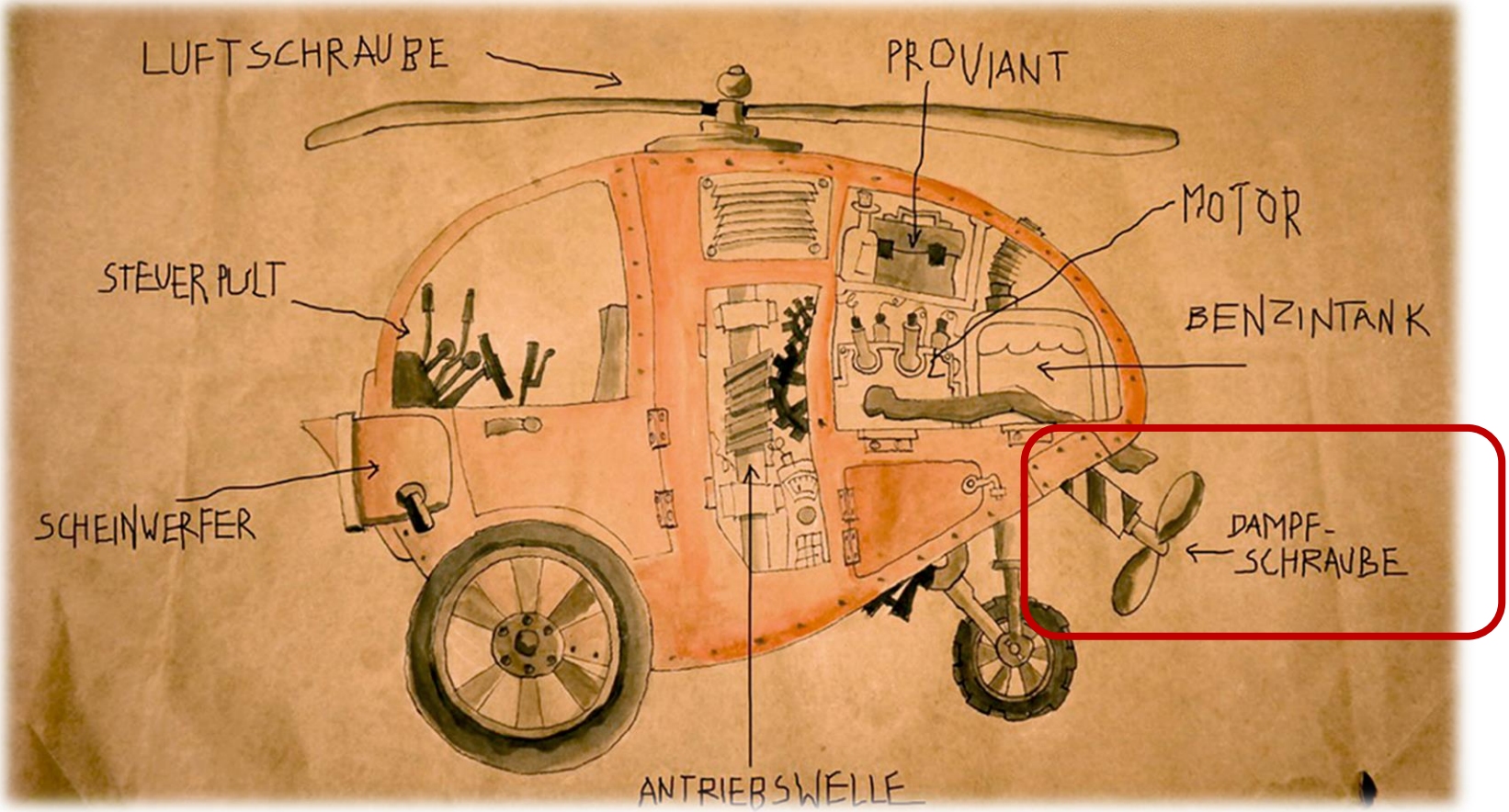
The Fliewatüüt



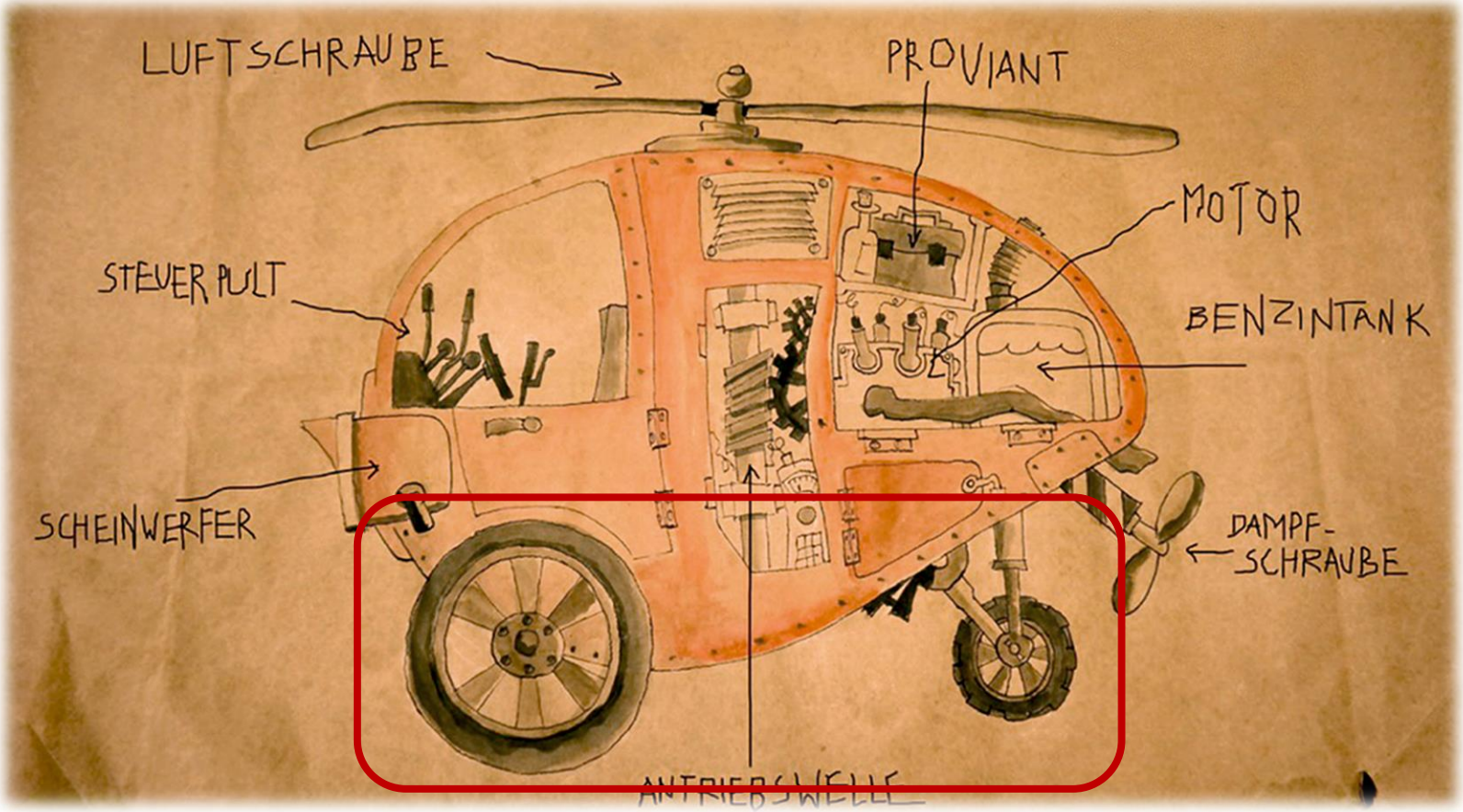
The Fliewatüüt



The Fliewatüüt



The Fliewatüüt



To get the regulatory approval you will need

- A preliminary testing program where you:

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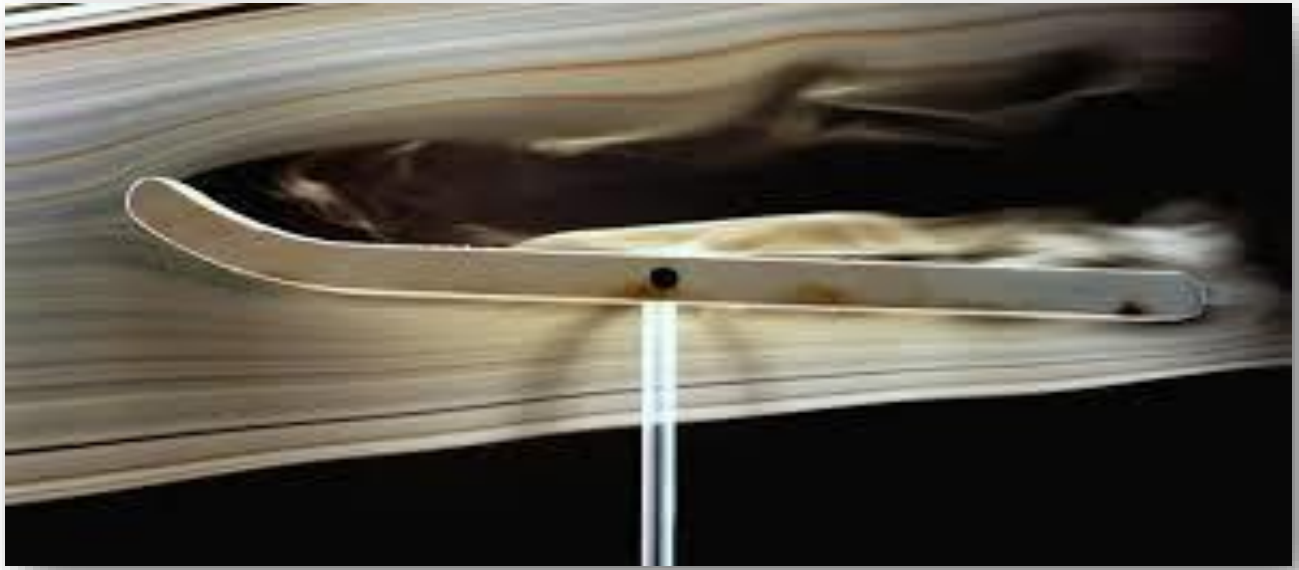
- A preliminary testing program where you:
- Test the aerodynamics of the invention in **wind** and water



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- A preliminary testing program where you:
- Test the aerodynamics of the invention in wind and water
- Provide testing of the **engine**

To get the regulatory approval you will need

- A preliminary testing program where you:
- Test the aerodynamics of the invention in wind and water
- Provide testing of the engine
- Build a prototype

You now probably talk to ‘someone’ and ask

- Should we develop this further?

You now probably talk to ‘someone’ and ask

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- If the answer is yes you do some more testing…

Phase 3 of your development

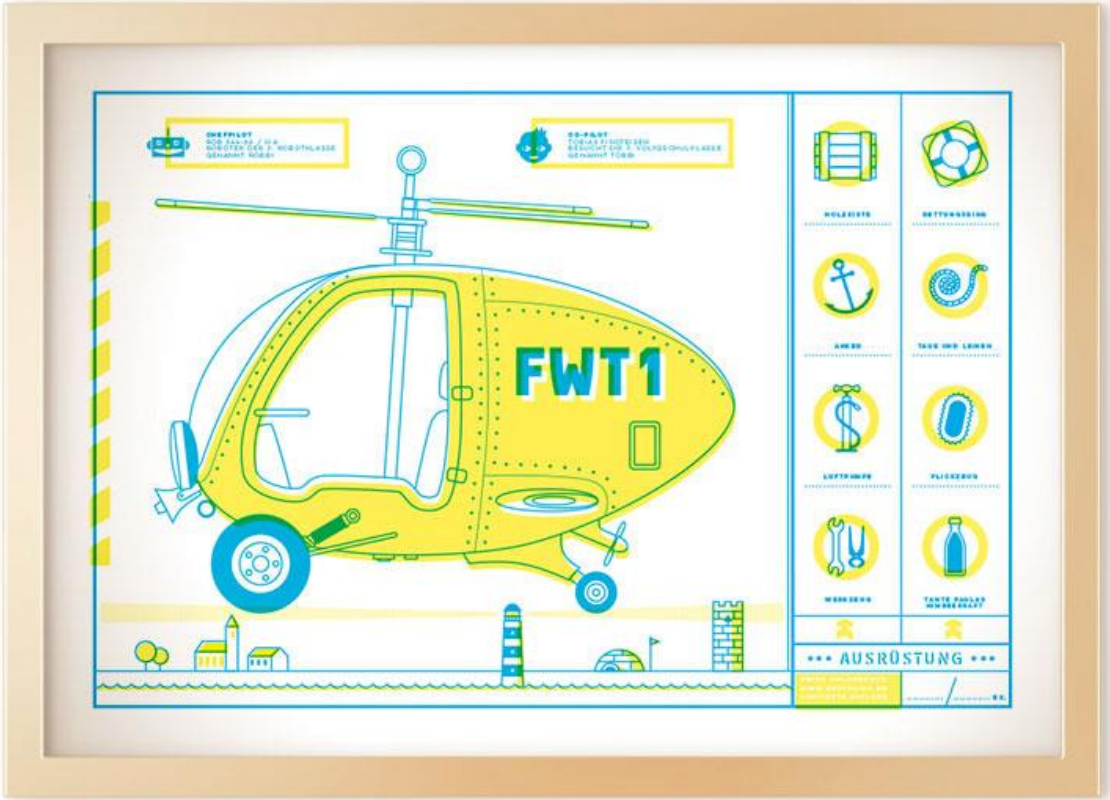
- You build an up-scale version close to the final product

You fly it around the Nevada dessert

You drive from Oslo to Trondheim

You cross the serene Lak of Mt Pinatubo

You provide a suitable safety instruction manual



Based on this evidence some ‘unnamed’ agency...

- ….will grant you the right to sell the Vehicle in all EU member states

But now the hard work actually begins!

If you ask the Germans to pay for this they will

- Want you to compare the driving abilities to a Mercedes, a VW, a BMW and a Opel.
- They declare to be not so interested in the added value of the Helicopter part because the German airspace is crowded as it is.
- The boating capabilities are questionable in their assessment because you tested on a lake, not a river.
- And anyhow, you vehicle doesn’t comply fully with regulations for either cars, helicopters or boats.
- But nonetheless you can sell it for one year in Germany anyhow!

If you ask the Italians to pay for this they will

- Want you to compare the driving abilities to a Ferrari or a Lamborghini.
- They declare to be interested in the added value of the Helicopter part but have no Italian build helicopter to compare with and ask you to find a suitable comparator.
- The boating capabilities are interesting, but you didn’t test it on the ocean, so they demand you do that in addition (preferably off the Adriatic coast).
- And anyhow, why is the thing so ugly (get a designer) and can it be purchased in different colours?
- If you want to sell it you need to set-up a database with info on how satisfied the users are.

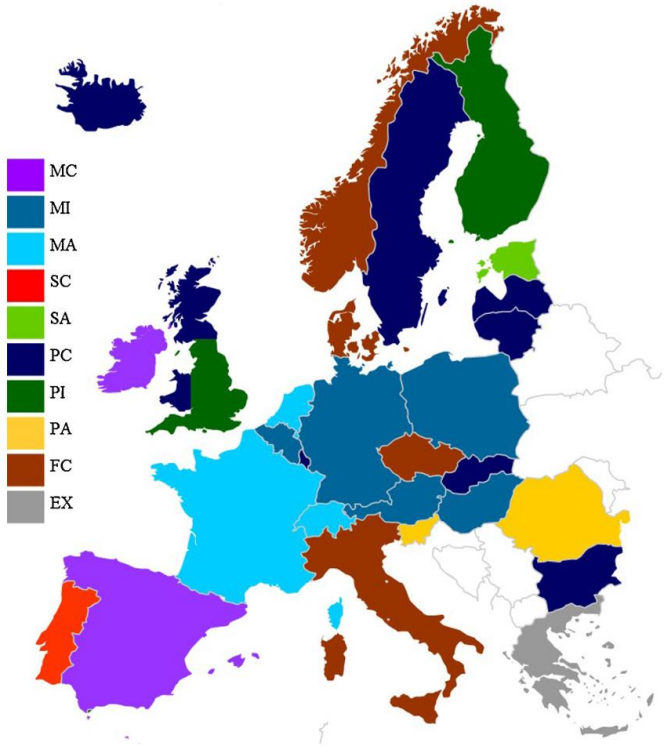
If you ask the British to pay for this they will

- Want you to compare the driving abilities to a suitable car representative for the British car industry.
- They declare to be interested in the added value of the Helicopter but want you to compare it to a Agusta Westland AW159 Wildcat built not later than 2013.
- The boating capabilities are interesting, but you didn't test it in the channel, so they demand evidence that your test is good enough to allow extrapolation to crossing the channel.
- And by the way, you need to provide support for the fact that testing was done in Nevada (too dry), Norway (too wet) and a shallow sweet water lake with no waves.

If you ask the NoMA to pay for this they will

- Want you to compare the driving abilities to a suitable car representative for Scandinavia, so maybe a Volvo or a Saab.
- They declare to be interested in the added value of the Helicopter but realize that the actual real world use in Norway is zero because our helicopters are usually grounded for various reasons.
- The boating capabilities are interesting, but you would have to provide data with the Hurtigruten boat as a comparator.
- And by the way, we agree with the British that you need to provide support for the fact that testing was done in Nevada (too dry), Norway (roads not very busy at 3 am) and a shallow sweet water lake with no waves (Fjord).

And remember, this is just the tip of the iceberg



The conclusion

- Getting regulatory approval requires evidence that can support testing in **ideal circumstances**, also known as the RCT.
- Reimbursement decisions has to take the actual context of how your product will be used **in the wild** into account, as well as it is about comparing the new with the old.
- It is this (real world) information that normally has to be provided by some additional data source other than the original RCT and is considered in a **national context**.

The conclusion

- Getting regulatory approval requires evidence that can support testing in **ideal circumstances**, also known as the RCT. **Internal Validity**
- Reimbursement decisions has to take the actual context of how your product will be used **in the wild** into account, as well as it is about comparing the new with the old. **Relative effectiveness**
- It is this (real world) information that normally has to be provided by some additional data source other than the original RCT and is considered in a **national context**. **External Validity**

Healthcare Technology Assessment (HTA)

- *is the systematic evaluation of the properties, effects, and/or impacts of health technology.*

Purpose- *to address the direct, indirect, intended, and unintended benefits and consequences of the adoption of healthcare technology .*

-Hailey, Babidge, Cameron, & Davignon 2010

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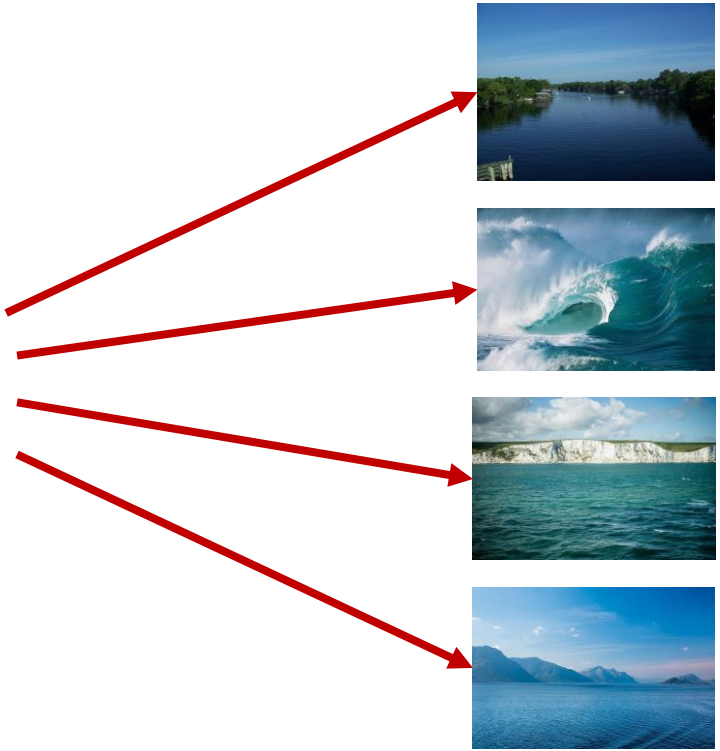
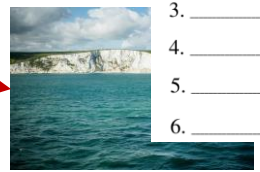
-Hailey, Babidge, Cameron, & Davignon 2010

But here is the biggest misunderstanding!



The PICO



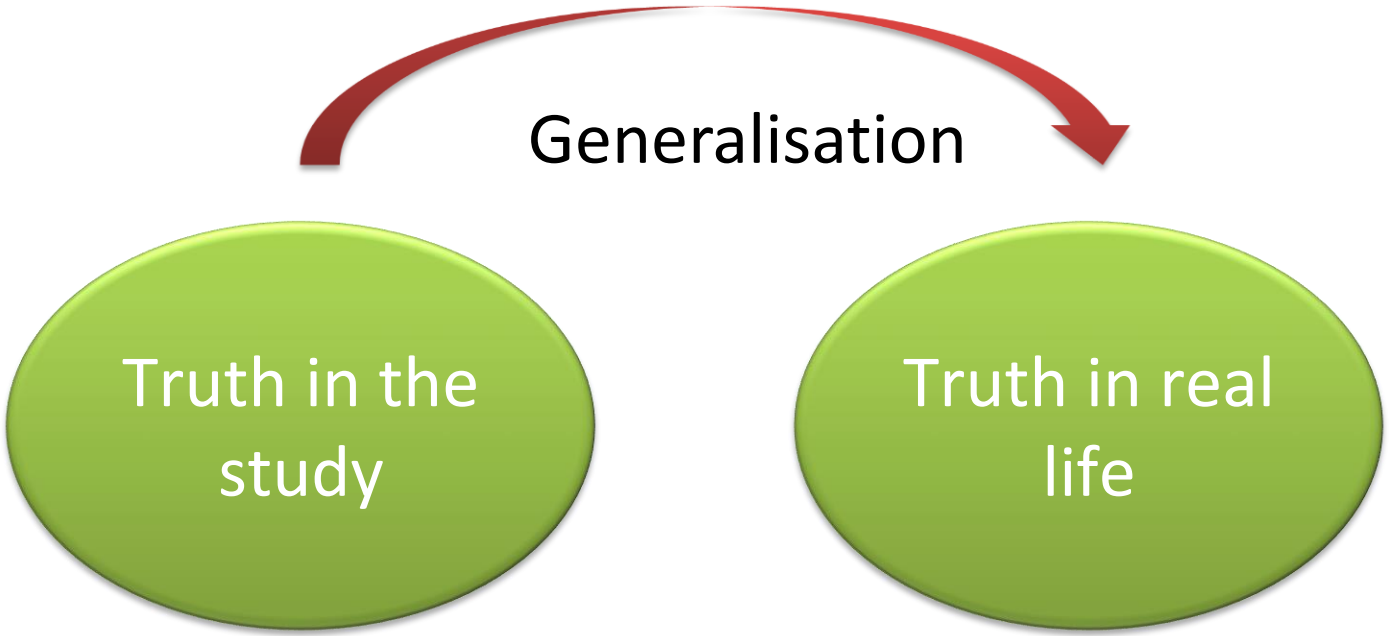

My List for Santa
Dear Santa,
I have been very good this year so I hope you will bring me the presents listed below. Thank you!
Love, _____
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
SantaTimes.com


HETEROGENEOUS

You are not Santa , you are supposed to do this

External Validity

Internal versus External validity



Internal Validity

External Validity

So which mistakes were made in the *Fliewatüüt* development program?

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- The development program focused to heavily on the regulatory approval

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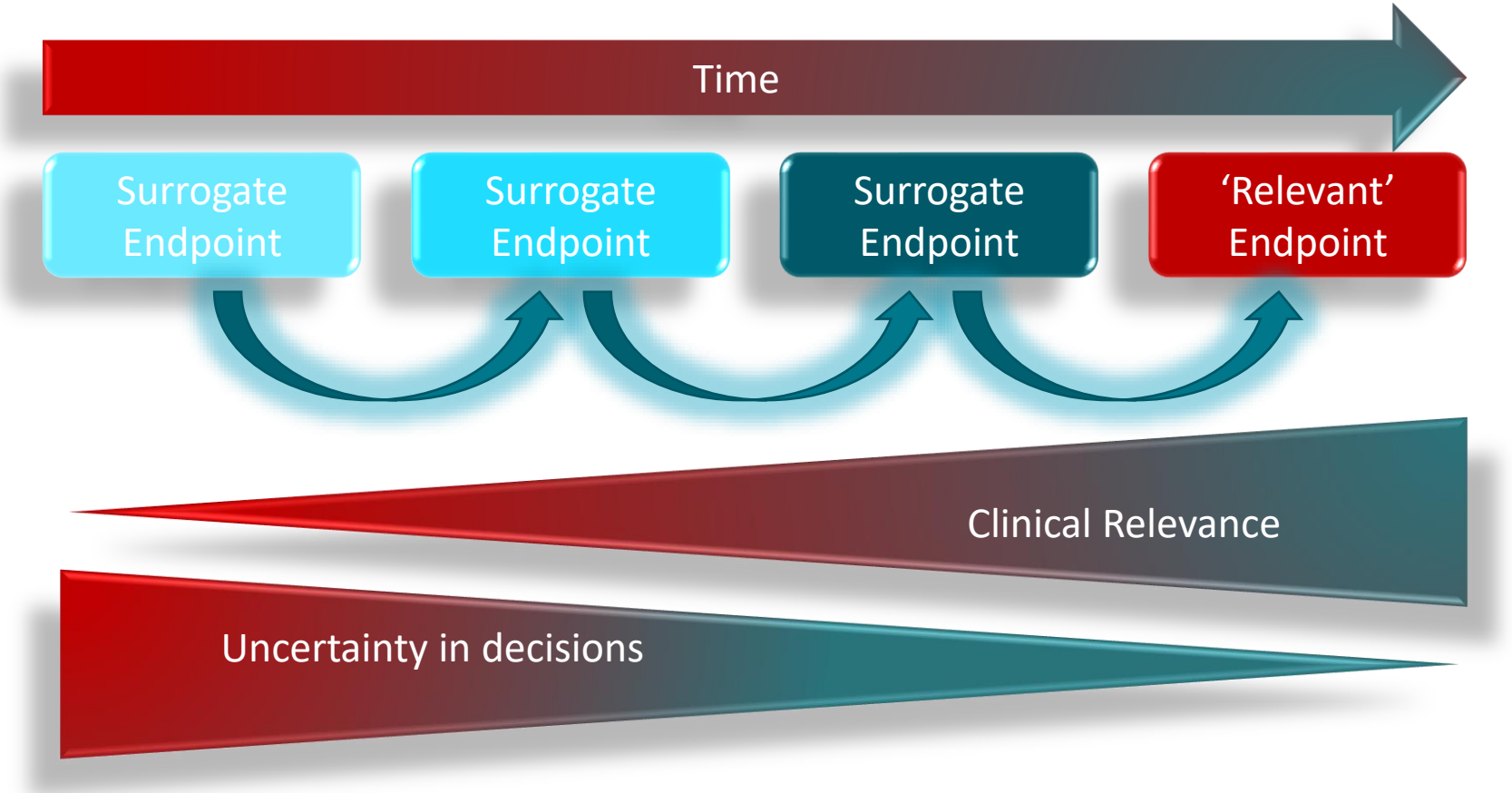
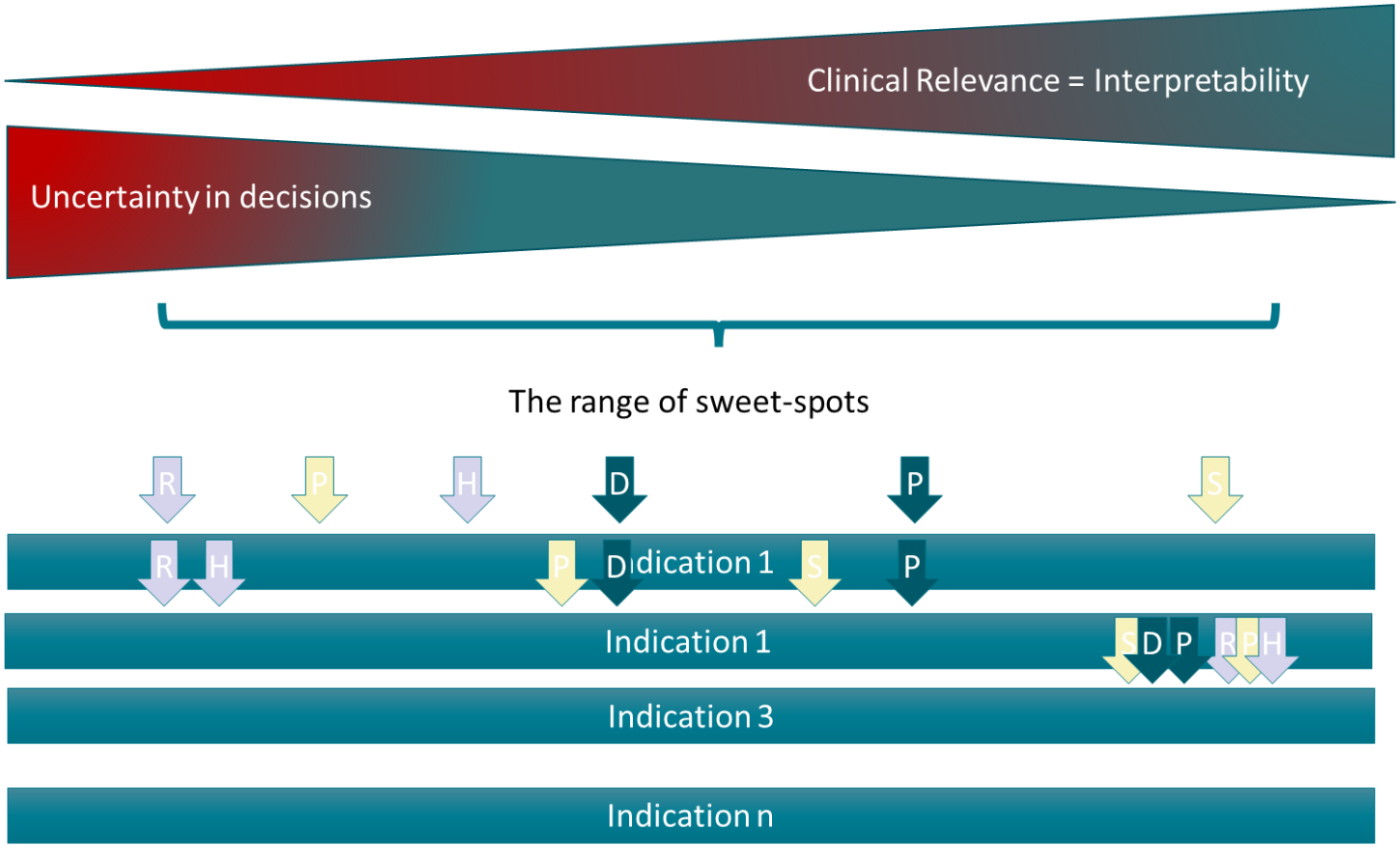
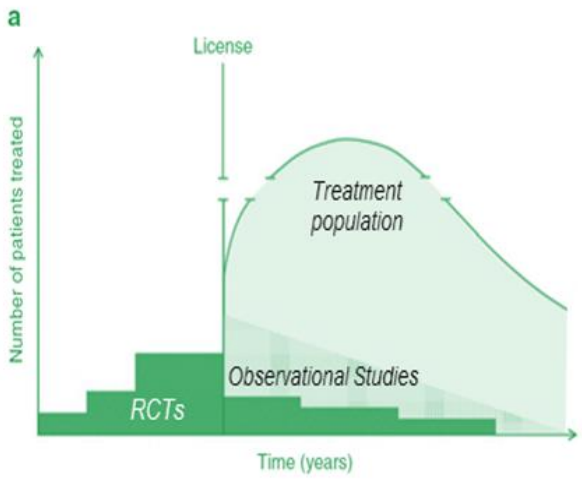
Uncertainty is piling up



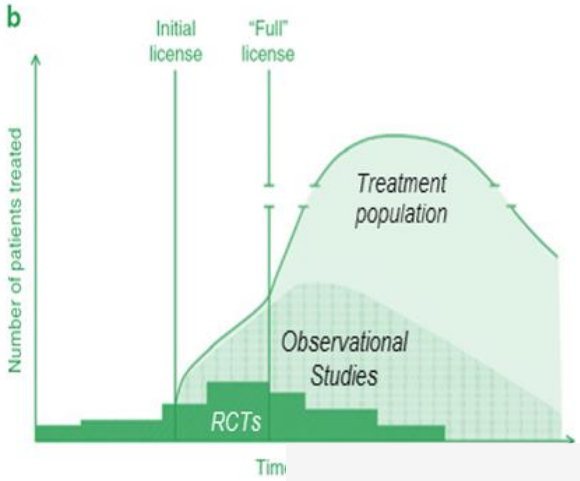
The Sweet-spot



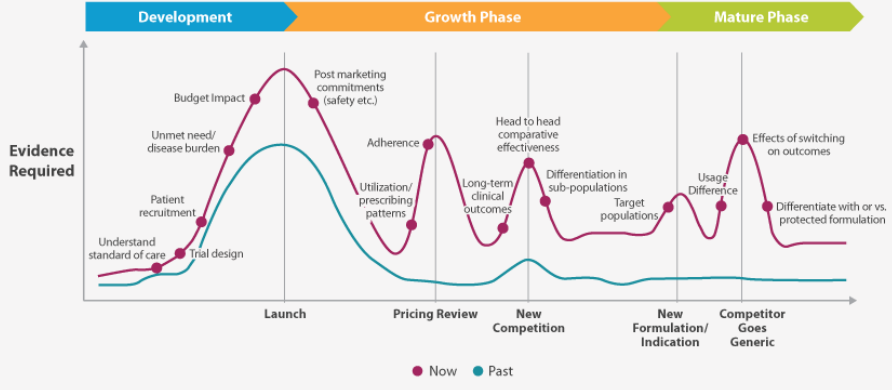
Conventional scenario

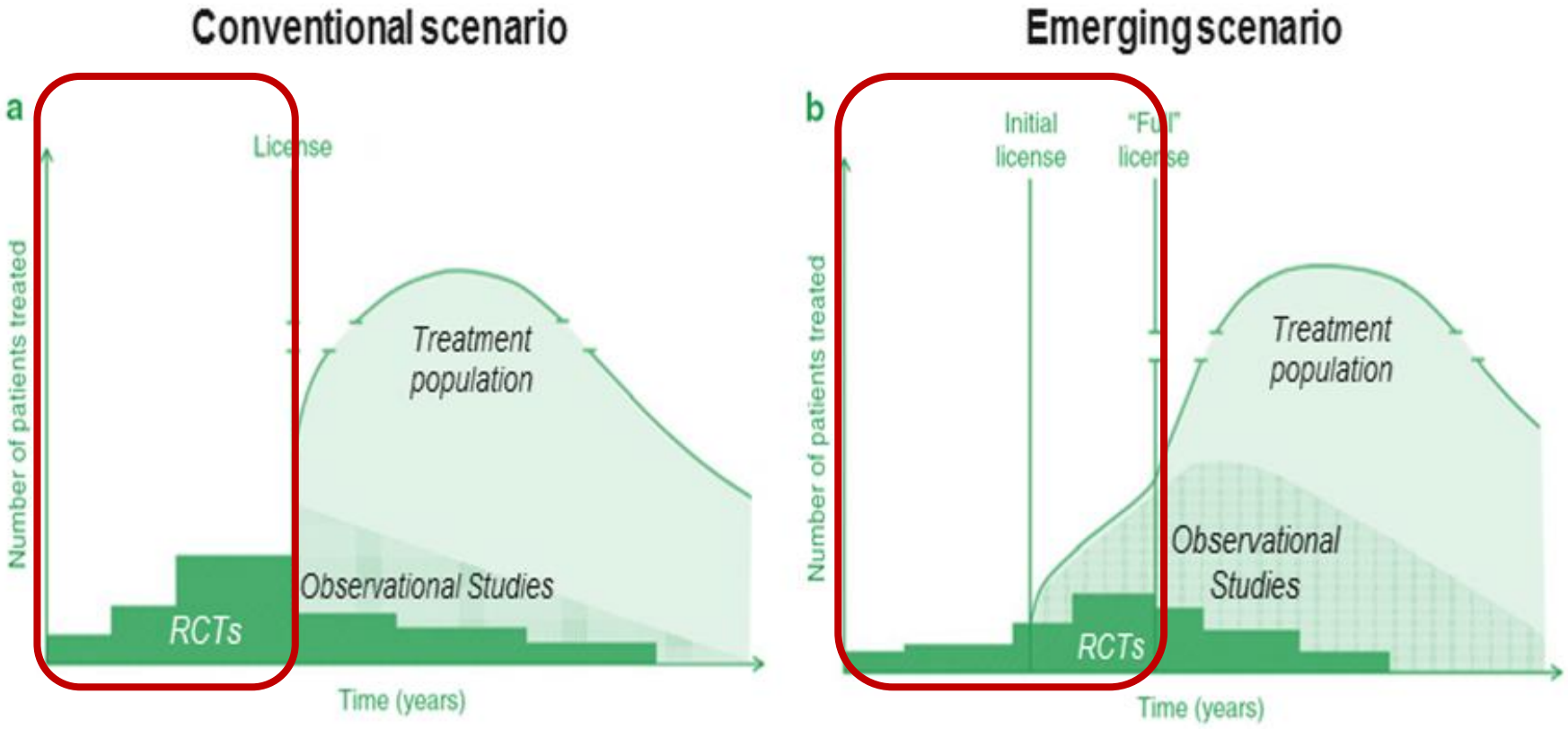


Emerging scenario



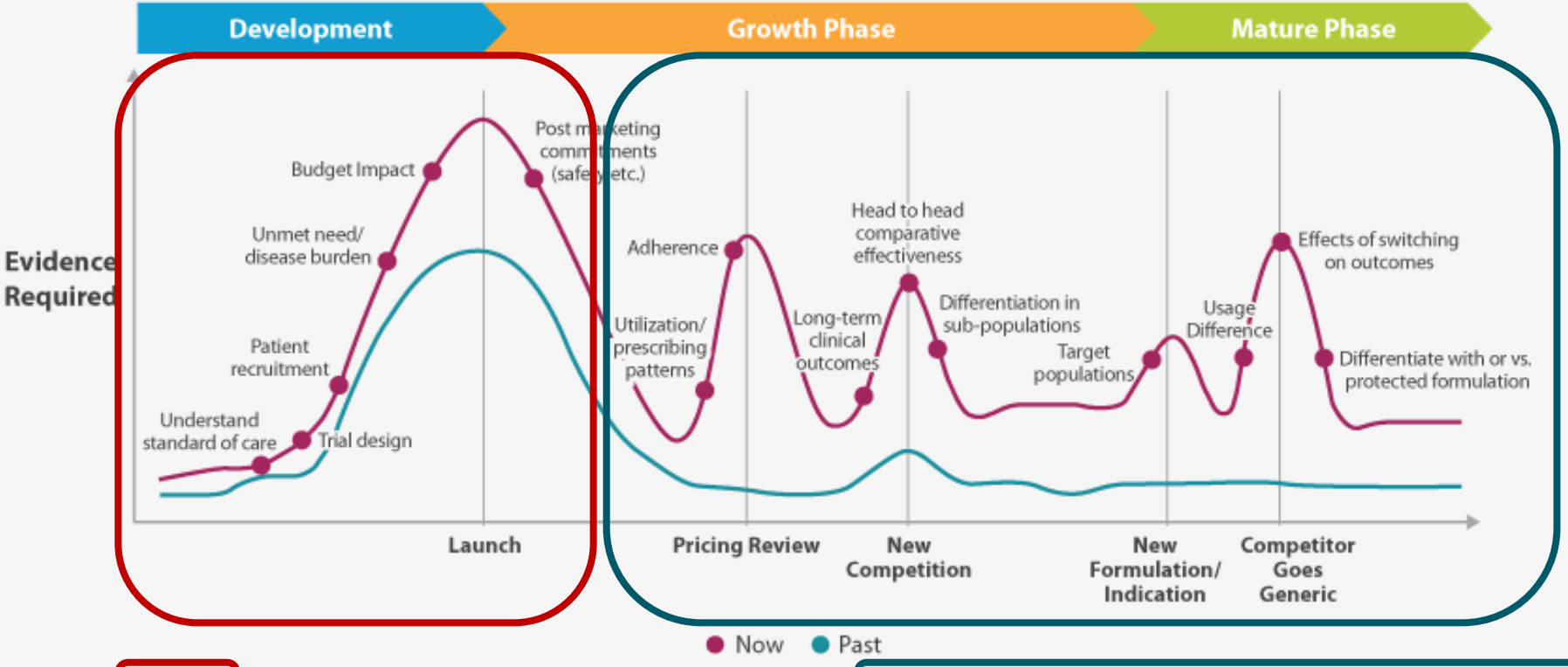
RWE Intensifying Across Product Lifecycle




Conventional scenario
a
License
Number of patients treated
Treatment population
Observational Studies
RCTs
Time (years)
Emerging scenario
b
Initial license
"Full" license
Number of patients treated
Treatment population
Observational Studies
RCTs
Time (years)

B/R

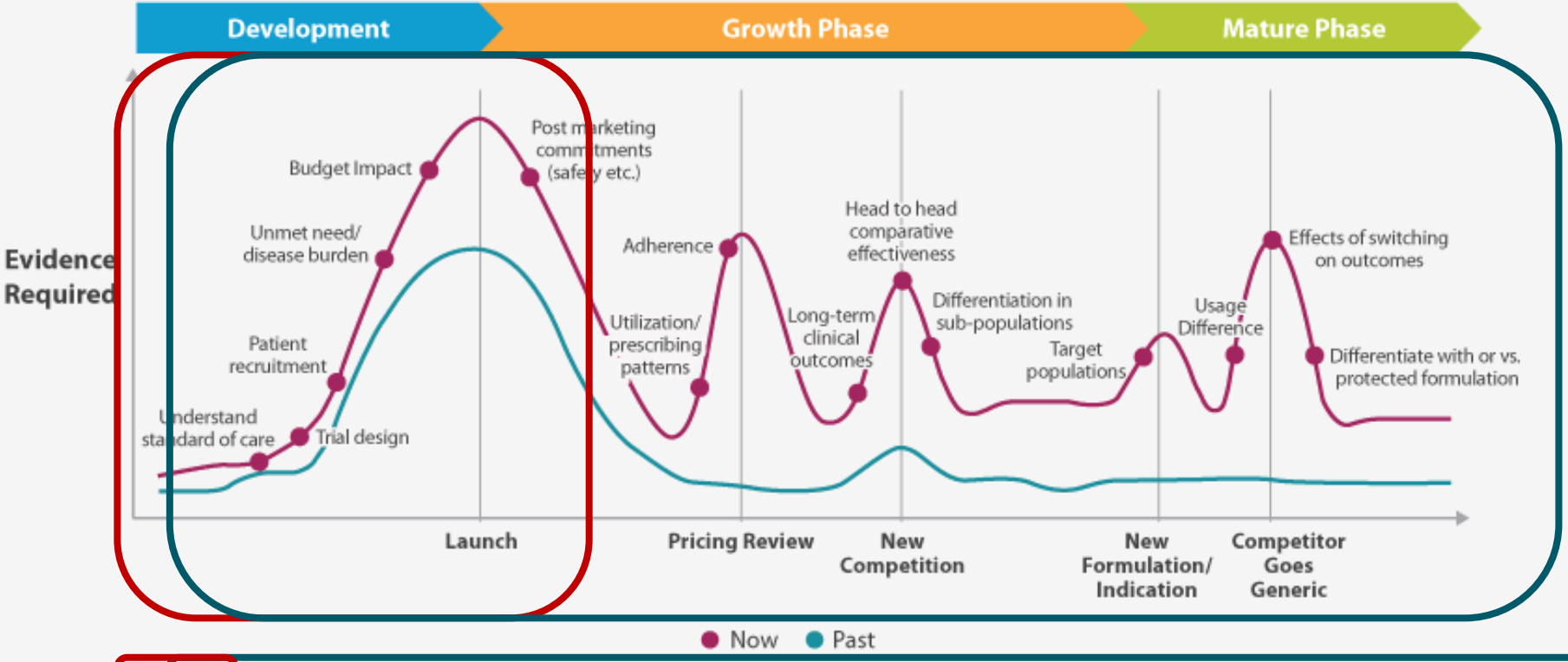
RWE Intensifying Across Product Lifecycle



B/R

HTA/Payers/Physicians/Patients/Families

RWE Intensifying Across Product Lifecycle



B/R

HTA/Payers/Physicians/Patients/Families

How do you want it - the crystal mumbo jumbo or statistical probability?

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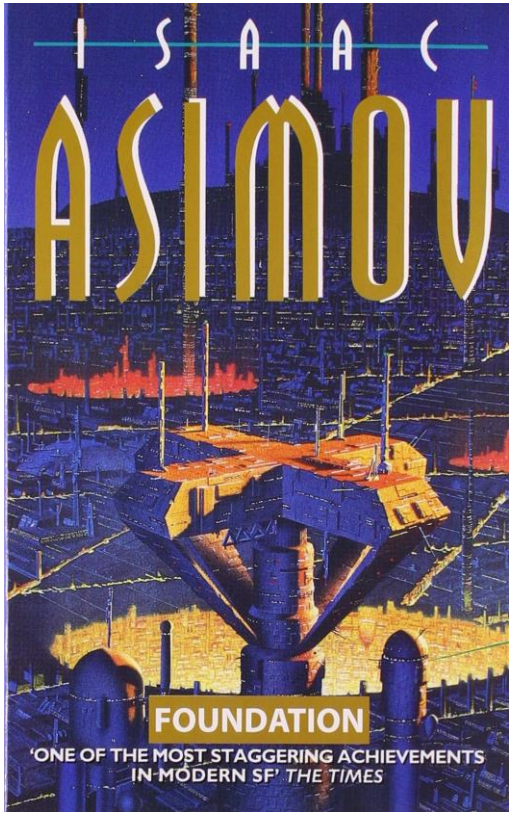


Hari Seldon: Mathematicians Predict the Future With Data From the Past

Poor prediction = Risk avoidance

- Risks also accumulate!
- Don't mistake uncertainty in evidence with uncertainty in the decision making

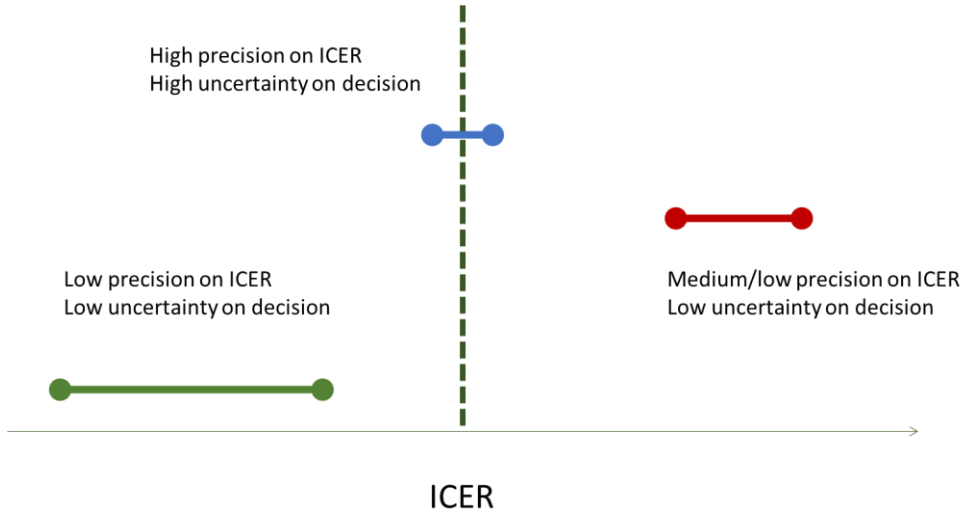


Figure modified from 'Hur ska vi utvärdera och hur skavi betala?', 2021; TLV Sweden

You now probably talk to ‘someone’ and ask…

- *Should we develop this further?*

➢ Is this happening?

➢ Probably not enough, even though we have tools such as JSC’s.

You now probably talk to ‘someone’ and ask…

- *Should we develop this further?*

➢ Is this happening?

➢ Probably not enough, even though we have tools such as JSC’s.

➢ Investing in JSC’s is investing into better submissions and saving time during the assessment!

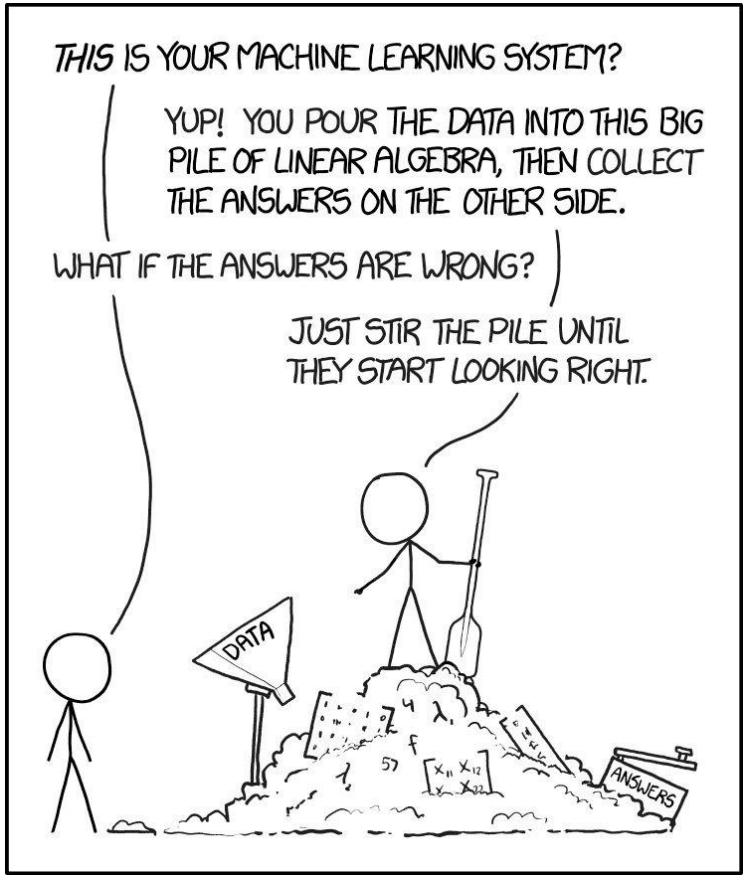
➢ It is not about alignment but about generating the right evidence to answer the question -> this is not always/only a RCT!

You need to start non-linear thinking!

Source: muhsinbudiono

https://www.slideteam.net/catalog/product/gallery/id/42682/image/305387/

Usually I watch my language…..




communicate with others.
I will effectively
communicate with others.
I will effectively
communicate with others.
grammarly
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