14TH CROATIAN COCHRANE SYMPOSIUM

APPROPRIATE PATIENT INVOLVEMENT IN HTA

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Rational: transparency and trust in scientific evaluations

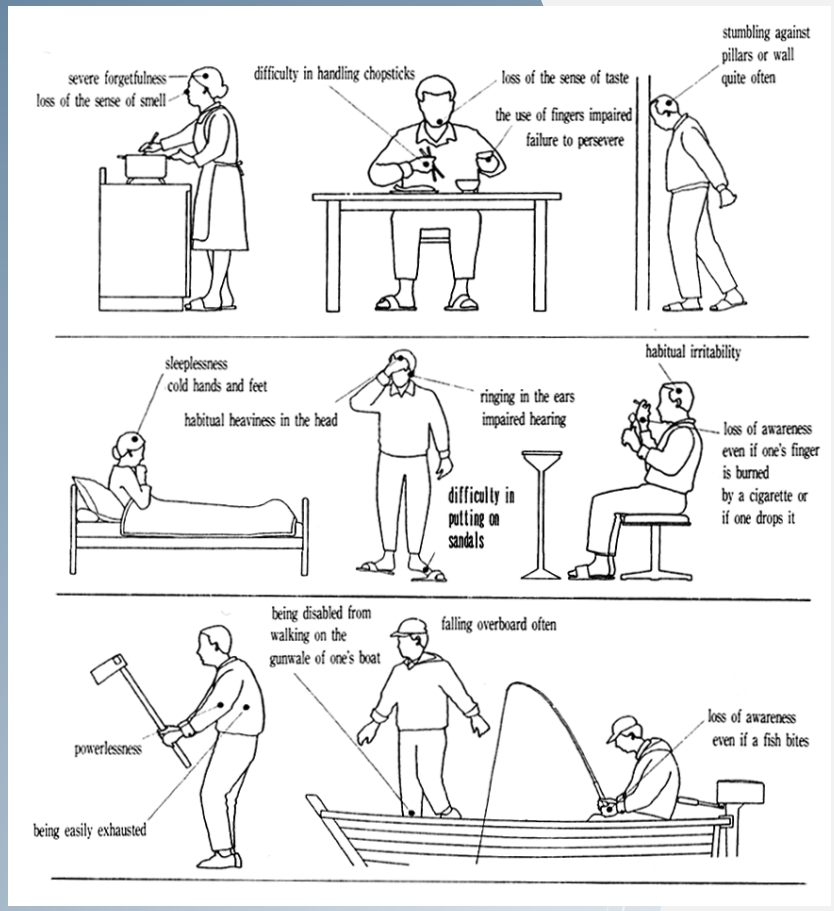
- In 2021, civil society takes part in most if not all scientific evaluations
  - Can you think of the Intergovernmental Panel on Climate Change (IPCC) without its 143 non-governmental organisations serving **as observers**?
    - With 193 UN members and thousands of scientists (see here https://www.ipcc.ch/about/structure/)
  - EMA: representatives of patients and consumers take part in more than 1100 medicine-specific activities, healthcare professionals in more than 370, including decision-making (members of scientific committees, management board) see https://www.ema.europa.eu/en/documents/report/stakeholder-engagement-report-2020-2021_en.pdf
- As **witnesses**, civil society representatives can understand how health technologies are assessed as insiders – without even contributing
  - Can understand how assessors work, their reasoning
  - Can see which data are used (or discarded)
  - Can check how procedures are respected
- This transparency represents a large part of the effort **to establish trust** between the public and HTA bodies

WHAT DO WE MEAN BY “APPROPRIATE”?

SEVERAL METHODS EXIST

WHICH ONE IS THE MOST APPROPRIATE FOR WHICH HTA PROCEDURE?

Same disease, different patients, different expectations



Analyse & Evaluate

- Engaging with civil society organisations and individual patients is a long-term commitment and a cultural endehavour

• The description of the technology and its use

If patients disagree how the technology was developed?

An oral formulation proposed to replace an injection one, where patients think the tablet should only used to bridge between 2 injections?

If you interview 1 or 2 patients, you can miss this feedback: the right person?

If you call for a public contribution using an online questionnaire, you can also miss it: your outreach?

• The impact on patients, results interpretation

When trial results failed to capture significant clinical benefit, but patient groups have other data to share?

France: more than 2,500 patient groups of which only 100 member of France-Asso-Santé

Online questionnaire open for only a short period – most groups unaware

But how can an HTA body engage with 2,500? Should they?

• Data not collected during R&D

An HTA is performed, concludes benefit to be minor, technology is reimbursed, and in fact data show benefit to be major?

Eg recent treatments authorised for cystic fibrosis

Months/years after, and for the first time, women can become pregnant, and hundreds/thousands can now give birth to a live child

Completely overlooked during initial HTA

How interactions are envisaged

- HTA set the domains where patients are expected to contribute, usually the "unique perspective of being a patient": "PICO"
  - Patients respond by interviews, questionnaires, participation in meetings…
- But this is not a two-way interaction, as patients might have their own concerns, issues, not included in the PICO
  - They might have other views on other aspects than the "PICO"
  - They might want to comment on organisational, ethical or legal aspects: is there space for this?
  - For example
    - Severe Combined Immune–deficiency due adenosine desaminase deficit (ADA-SCIID)
    - SOC: allogenic bone marrow transplantation
    - If no compatible donor can be found: gene therapy (Strimvelis®)
    - NICE, UK: "Access to Strimvelis may reduce the disparity in wait times for transplant between different ethnic groups"

HOW CAN WE BEST INVOLVE PATIENTS?

LEARNING FROM OTHERS

Patients can be consulted on:

- HTA early dialogues (scientific consultation / advice)
  - To minimise the risks that inadequate information are submitted at a later stage
- Scoping
  - Which domains/topics/questions should be answered?
  - Which patients to benefit? Which intervention? Which comparator? Which relevant outcomes to consider?
- Assessment
  - Providing the answers: how does the technology compare with available treatments?
  - How reliable are the results of clinical studies?
- (Appraisal)
  - Making the decision to cover/reimburse
  - (Price negotiations)

Theoretical stages for the involvement of external experts

Halmed

Find experts — Call: information –> Disseminate the call and select the right people

Prepare experts — Explain the procedure –> administrative tasks (Conflicts of interest, confidentiality…)

Involve experts — Achieve the interaction (meetings / questionnaires / interviews / focus groups / citizens' jury / aggregated data…)

Elaborate Input — Adjustment and insertion in reports – Follow-up

Acknowledge Input — Feedback – Measurement - Visibility

Methods to catch patient input

Focus groups / patient jury

5-10 people

Preliminary phase: **Scoping**

With assessors (and sponsor)

Free speaking

Divergences

Meetings (F2F, online)

1-2 people

With various experts (and sponsor)

Direct interaction with different experts

Logistic preparation and **administrative** tasks

Specific questions first: **preparation** needed (reading)

Interviews

One to one

Semi-guided questions

Addition and follow-up possible

Be prepared on examples

(national language)

Questionnaires

For large audiences

Based on existing templates

No interaction : one shot
No follow-up

Dissemination

(national language)

IMPACT

2016: *Idebenone (RAXONE) for Leber's Hereditary Optic Neuropathy* (Scottish Medicines Consortium)

SMC is one of the most advanced HTA body in Europe for capturing patient views

Indication: visual impairment in adult and adolescents (vision not fully damaged yet)

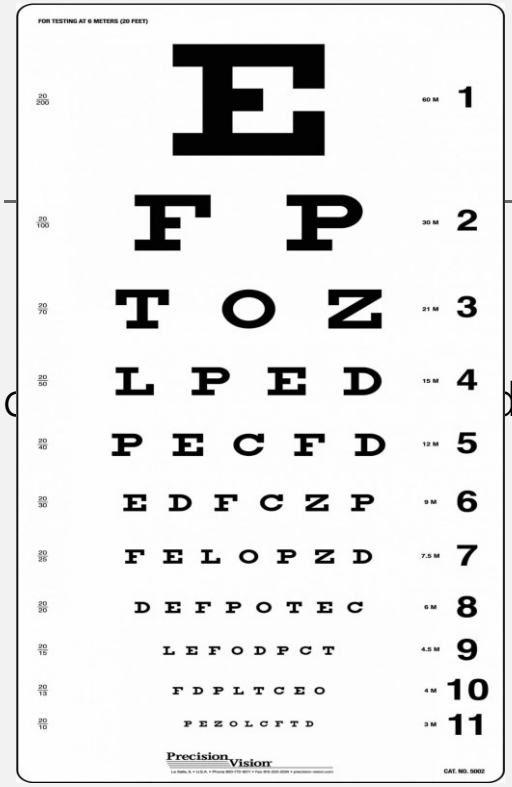
- Sponsor

CT: some progress with eye chart

Claimed "vision recovery"

Price proposed:
100.000 £ / patient / year

(116.000 €)



- Outcome

SMC used the opinion of patients during price negotiations

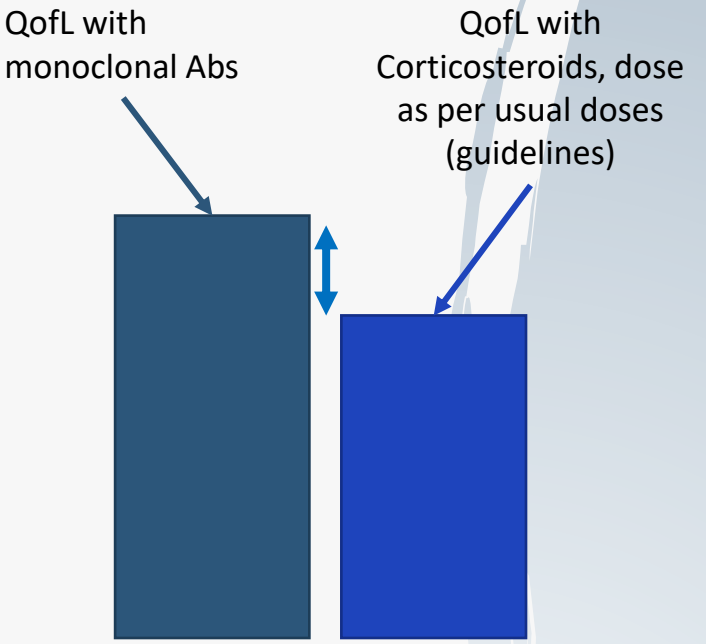
30% discount on final price: (with a performance-based agreement)

Relevant outcome measure proposed by patients: *% who can go on the street unaccompanied*

Curtesy Russell Wheeler, LHON Society, UK

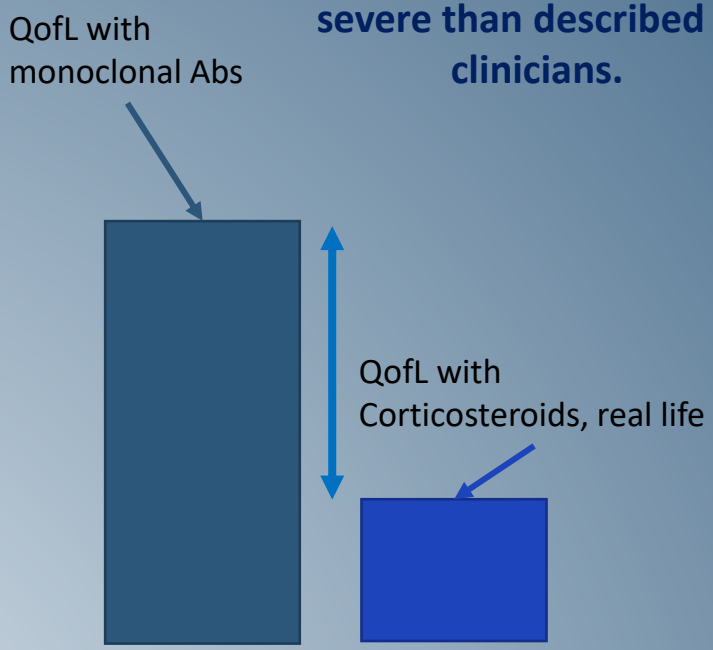
NICE, Crohn's disease, infliximab and adalimumab

Initially compared to cortico-steroids



Cost per QALY utility analysis: Monoclonal Ab not cost-effective

Patients reported they were using much higher corticosteroids doses. ADRs were much more severe than described by clinicians.



A different comparator than corticosteroids had to be used

Curtesy François Magnen, formerly NICE, UK

EDUCATION FOR PATIENTS AND PATIENTS GROUPS

IS THE KEY FOR APPROPRIATE INVOLVEMENT AT INTERNATIONAL (JSC AND JCA) AND NATIONAL LEVEL

Trainings for patients and for healthcare professionals

Not exhaustive

DIU Clinical trials in Rare Diseases

Universities of Lille, Dijon, Lyon

For patients' advocates and healthcare professionals

105 hours

Clinical research, R&D, evaluation and regulation of medicines

E-learning and onsite

EUPATI Patient Expert Training Programme

https://learning.eupati.eu

27 modules, + 8 days = **75 hours**

Clinical development, regulatory affairs, HTA

E-learning and onsite

EURORDIS Summer School Rare Diseases

https://openacademy.eurordis.org/summerschool/

For patients' advocates & academics

23 hours e-learning + 5 days = **57 hours**

Clinical development, regulatory affairs, HTA, pharmacovigilance

HTADS International Continuing Education

https://www.umit-tirol.at/page.cfm?vpath=departments/public_health/htads-continuing-education-program/introduction-to-health-economics-and-hta

Modeling Approaches for HTA 3 days **50 hours**

Introduction to Health Economics and Health Technology Assessment 3 days **50 hours**

LSE Principles of HTA

https://www.lse.ac.uk/resources/calendar/courseGuides/HP/2021_HP4D2E.htm?from_serp=1

20 hours

Lectures and seminars: half a unit

Part of a 2-year programme

EU Project Call for training patient and clinicians (in progress)

A 2-year project

Training content and sessions, list of first trained experts, list of eligible organisations to work with, awareness activities

HTX project: Next generation HTA

https://www.htx-h2020.eu/

POTENTIAL BARRIERS OF PATIENT INVOLVEMENT IN HTA IN CEE COUNTRIES

Dimitrova et al. Potential Barriers of Patient Involvement in Health Technology Assessment in Central and Eastern European Countries. Front Public Health. 2022;10:922708.

https://doi.org/10.3389/fpubh.2022.922708

	Categories	Potential barriers
PAYER/HTA BODY PERSPECTIVE	Limited willingness to involve patients	- Limited impact of societal factors on pricing and reimbursement decisions (i.e., the reimbursement decision i evaluated only from the payer perspective per legal framework) - Lack of understanding of the added value of involving patients in the HTA process - General lack of trust in the objectivity and relevance of "patient stories" (e.g., fear of emotional aspects negativel affecting the decision-making process) - Patient involvement in HTA is not mandatory/is not mentioned in the local HTA guideline
	Conflict of interest & confidentiality	- Fear of potential conflict of interest issues due to industry funding of patient organizations - Fear of the violation of confidentiality by patient representatives
	Difficulties to finding the "right" patient representative	- Lack of support and supporting tools (e.g., registries or network) to help patient recruitment - Difficulty to identify representatives from the disease area needed (e.g., some patient communities may hav "louder voices" than others) - Lack of understanding of different patient roles (whether the patient is representing their own views or their patier community's) - Patient representatives might not be representative of the whole patient community in terms of socioeconomic status and other basic characteristics (e.g., higher educated, somewhat younger, health-literate patients tend to take on these roles)
	Lack of human resources at relevant public institutes	- Fear of the patient involvement process needing too much support time amidst the tight HTA decision timelines - Payer or HTA organizations do not have enough human resources/time to involve patients (even though they would intend to)
	Not knowing how to involve patients	- Lack of experience/training/skills from the HTA and payer organizations' side in knowing how and when t incorporate patient perspectives - Lack of local (regional or country-specific) guidelines on best practices of patient involvement to HTA
PATIENT PERSPECTIVE	Lack of understanding the decision context	- Patient representatives' lack of basic knowledge in HTA - Patient representatives' lack of knowledge of the local regulatory processes including how they can get involved - Patient representatives' lack of knowledge in the medical language - Patient representatives do not speak/understand English which limits the amount of information (training, other countries' experience, scientific literature) they can access
	Lack of knowledge and guidance of evidence-based advocacy	- No methodological guidance to support the activities of patient organizations in collecting data (e.g., survey valuable for HTA - Patients' lack of experience in searching and/or interpreting information from independent resources (i.e., scientific articles)
	Lack of resources to be spent on meaningful patient representation	- No fair compensation for time offered and logistics issues (e.g., traveling time and costs, documents not sent o time for review, preparatory calls or meetings during working hours) -General lack of capacities due to financial constrains
	Lack of ethical guidance for representativeness	-No clear rules on how to represent a patient community and how to distinguish it from representing their individual patient perspective plus confidentiality prevents patient representatives from discussing/sharing views with others before attending HTA procedures/meetings

OTHER METHODS: PATIENT PREFERENCES ELICITATION

FOR THE NEAR FUTURE?

Natalizumab case study

Active drug	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effects	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved 2005 Marketing Authorisation suspended 2006 Re-introduced because of patient demand 2009 CHMP reassessed the PML risk
Data source	EPARs
Comparators	Placebo, interferon β-1a, glatiramer acetate

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (IMI PROTECT)
Led by the EMA with 31 public and private partners, 2009-2014

Work Package 5: Develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports

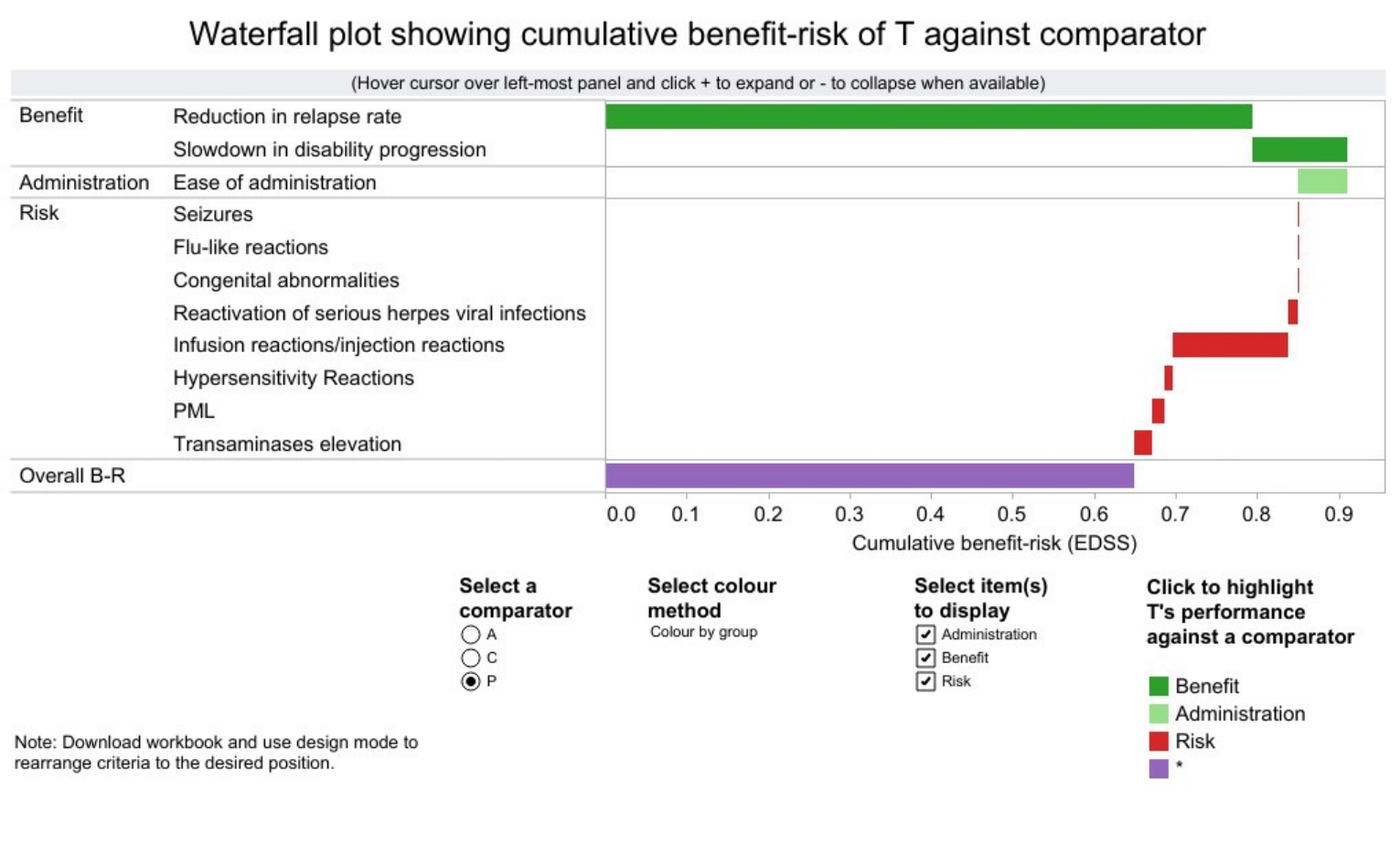
Prof Deborah Ashby OBE FMedSci, Professor of Medical Statistics and Clinical Trials, School of Public Health, Imperial College London

Example of comparing treatment option

Treatment features	Treatment A	Treatment B
Number of relapses during the next 5 years	4 relapses	2 relapses
Time (from today) until your MS gets worse	3 years	3 years
Chance of dying from liver failure within 10 years	None would die	20 patients out of 1000 (2%) would die
Chance of dying or severe disability from PML within 10 years	5 patients out of 1000 (0,5%) would die	None would die
Chance of dying from leukaemia within 10 years	None would die	None would die
Which treatment would you choose?	Treatment A?	Treatment B?
	50%	50%

Natalizumab: Criteria contribution

Waterfall plot for Natalizumab vs. placebo

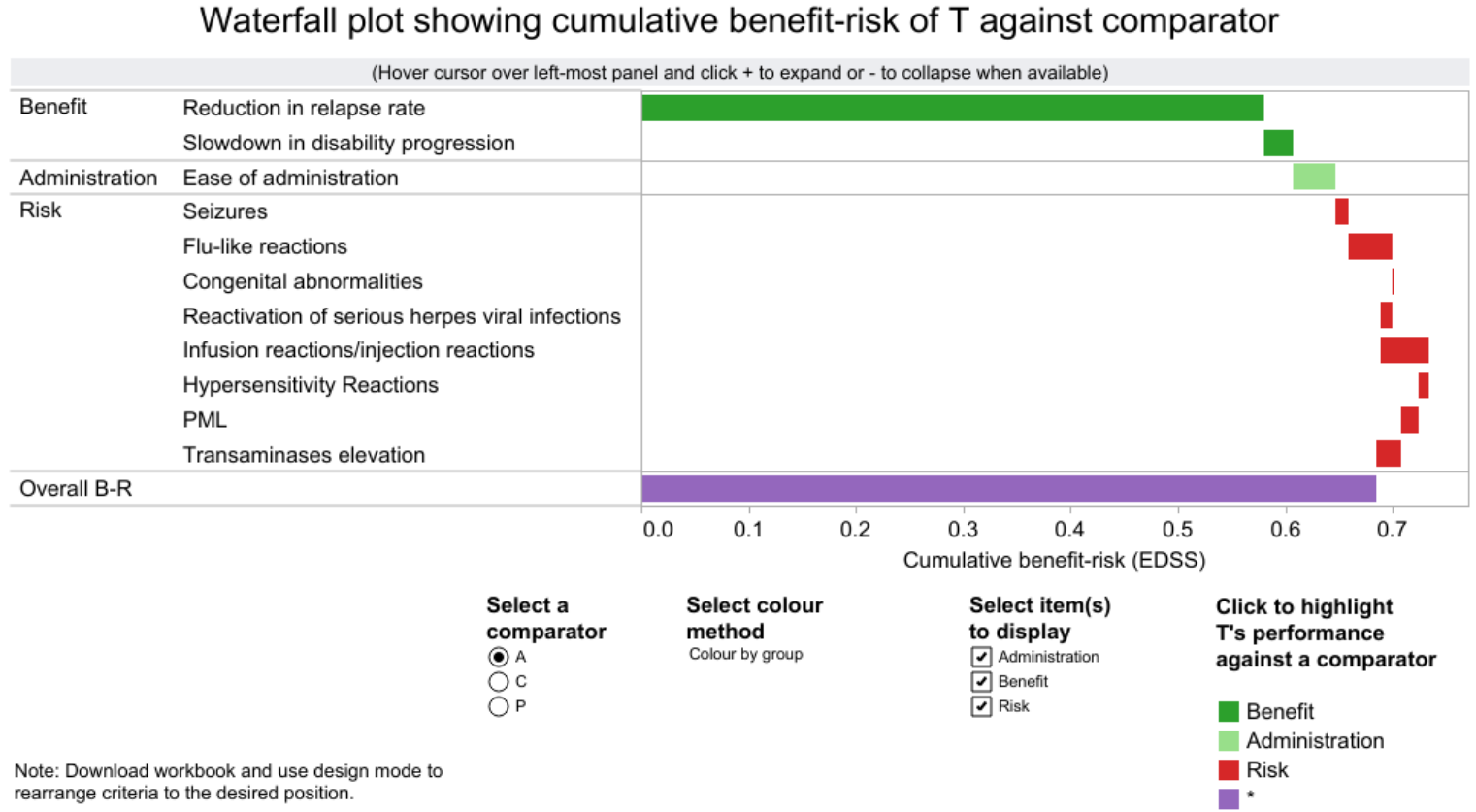


http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk

- The end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.

Natalizumab: Criteria contribution

Waterfall plot for Natalizumab vs. A



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Conclusion

Patient involvement in HTA

Engaging with patients, consumers, healthcare professionals is first a matter of transparency

When external experts contribute to HTA, the quality of the assessment is improved (IQWIG)

How can HTA assessors best verify they understand the clinical features of a disease?

For an effective involvement of patients, training activities are essential

THANK YOU

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