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Using Statistical Theory, Epidemiology and Clinical Trials for Public Health Impact

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Outline

- Pancreatic enzymes and fibrosing colonopathy
- SSRIs and suicidality
- PROTECT: Risk-benefit Decision Making for Drug Regulation

- Reflections

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Fibrosing Colonopathy in CF

- Apr-Oct 1992 - high strength pancreatic
- enzyme preparations introduced to UK.

- July-Sept 1992 - first cases of fibrosing colonopathy observed in Liverpool, UK, in boys who had recently switched to high-strength.

- Jan-Apr 1994 - more cases identified in UK and elsewhere

Epidemiological Studies: Aims

1. To establish incidence of fibrosing colonopathy in CF population in the UK
2. To determine whether fibrosing colonopathy was a new entity in the UK population
3. To identify factors associated with fibrosing colonopathy

Smyth, Ashby et al, *Lancet* 1995

Age	Males	Females
0-4	6/692	0/610
5-9	5/704	1/674
10-14	1/670	1/549
15+	0/1336	0/1045
Total	12/3402	2/2878

Incidence of fibrosing colonopathy

Case-control study

	Low Strength		High Strength	
	No	Yes	No	Yes
Controls	19	37	11	45
Cases	7	7	0	14

Enzyme usage

12 months prior to surgery

Case-control study

	0-4000	-8000	-12000	-16000	-20000	-24000
Controls	31	15	8	1	1	0
Cases	0	3	7	1	2	1

Cumulative high strength capsule intake

12 months prior to surgery

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12 month Enzyme Usage: Individual Products At any time

	OR	95% CI	P
Low Strength			
Creon	0.16	(0.03, 0.9)	0.4
Nutrizym GR	-	(,)	-
Pancrease	2.11	(0.54, 8.23)	0.3
High Strength			
Creon 25000	0.38	(0.10, 1.42)	0.15
Nutrizym 22	43.8	(2.51, 751)	0.01
Pancrease HL	8.4	(1.95, 36.1)	0.004

Main Conclusions

1. Study confirms the association with high-strength pancreatic enzyme usage.
2. Strong dose-response association for the main constituents (protease, amylase, lipase).
3. Brand differences are observed: there is an assocation with Pancrease HL and Nutrizym 22, but no association with Creon 25000.
4. Cases used more concomitant medication.

Do high-strength pancreatic enzymes cause fibrosing colonopathy?

- strength of association - absolute and relative
- consistency – US study not as clear-cut
- specificity - no reports in non-CF non-PE children
- temporality – OK? but reverse causality possible
- biological gradient (dose-response) - dramatic
- plausibility - ??coating ???effects of lipase etc
- coherence – problem now disappeared
- experimental evidence - no
- analogy - no

Treating Cystic Fibrosis

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The Secrets of Seroxat

- “Seroxat is one of the world's biggest selling and most successful anti-depressants. But this Panorama investigation discovers the drug may have a darker side - the programme reports that people can get hooked on it, suffering serious withdrawal symptoms when they try to come off it. For some it can lead to self harm and even suicide. But little warning of these possible side effects accompanies the drug. These are accusations that the drug's maker GlaxoSmithKline denies.”

news.bbc.co.uk

SSRI Expert Working Group- Remit

- Behavioural disorders, particularly suicidal behaviour, suicide attempts and suicide, and a possible causal link with SSRI's
- Withdrawal reactions and possible dependence
- Dose-response
- Patient Experiences
- Advise on product information, communication and advise CSM of conclusions

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Data released by MHRA Dec 2003 (placebo controlled RCTs: children and adolescents)

SSRI	Duration of trials	Outcome	OR (95%CI)
Fluoxetine	8 wks	Suicide attempts	1.3 (0.4, 4.4)
Sertraline	10 wks	"Suicide related events" (incl sui thoughts)	2.4 (0.5,12.4)
Citalopram	8-10 wks	Self harm	1.6 (0.8 to 3.5)
Paroxetine	8-12 weeks	"Possibly related to suicidality")	1.5 (0.6 to 3.7)
POOLED ESTIMATE			1.6 (0.8 to 3.5)

Gunnell & Ashby, BMJ 2004

GPRD Study 1995-2001, Nested case-control: n=146,095 (Martinez et al, BMJ 2005)

	Crude OR	Fully adjusted OR*
Suicide (n=36)		
Tricyclics	1.0 (ref)	1.0 (ref)
SSRIs	0.59 (0.28 to 1.27)	0.57 (0.26 to 1.25)
Non fatal self harm (n=1344)		
Tricyclics	1.0 (ref)	1.0 (ref)
SSRIs	0.97 (0.85 to 1.12)	0.99 (0.86 to 1.14)

*Adjusted for severity of depression, time of depression diagnosis in relation to start of therapy, referral to psychiatrist or psychologist prior to index day, past history of self-harm, diagnosis of or treatment for anxiety or panic disorder, schizophrenia, antipsychotic medication, drug misuse and alcohol abuse.

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GPRD Study 1995-2001, Nested case-control: n=146,095 stratified by age (p (interaction) =0.02) (Martinez et al, BMJ 2005)

	Crude OR	Fully adjusted OR*
10-18 years		
Tricyclics	1.0 (ref)	1.0 (ref)
SSRIs	1.73 (1.10 to 2.72)	1.59 (1.01 to 2.50)
19-30 years		
Tricyclics	1.0 (ref)	1.0 (ref)
SSRIs	1.00 (0.79 to 1.27)	1.04 (0.82 to 1.32)
>30 years		
Tricyclics	1.0 (ref)	1.0 (ref)
SSRIs	0.83 (0.69 to 1.01)	0.86 (0.71 to 1.04)

*Adjusted for severity of depression, time of depression diagnosis in relation to start of therapy, referral to psychiatrist or psychologist prior to index day, past history of NFSH, diagnosis of or treatment for anxiety or panic disorder, schizophrenia, antipsychotic medication, drug misuse and alcohol abuse

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Do SSRIs cause suicidality in children?

- strength of association - low
- consistency – between RCT and observational
- specificity - no
- temporality – in the right direction
- biological gradient (dose-response) – no evidence
- plausibility - ??various theories
- coherence – apparent discrepancies with trends
- experimental evidence – yes, from RCTs
- analogy - no

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Commission on Human Medicines, January 2011

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The licensing challenge

- The task of regulators (e.g. EMA, FDA) is to make a good and defensible decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making, and especially more modern methods of graphical display help regulators do these better?

Acknowledgements

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.
- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

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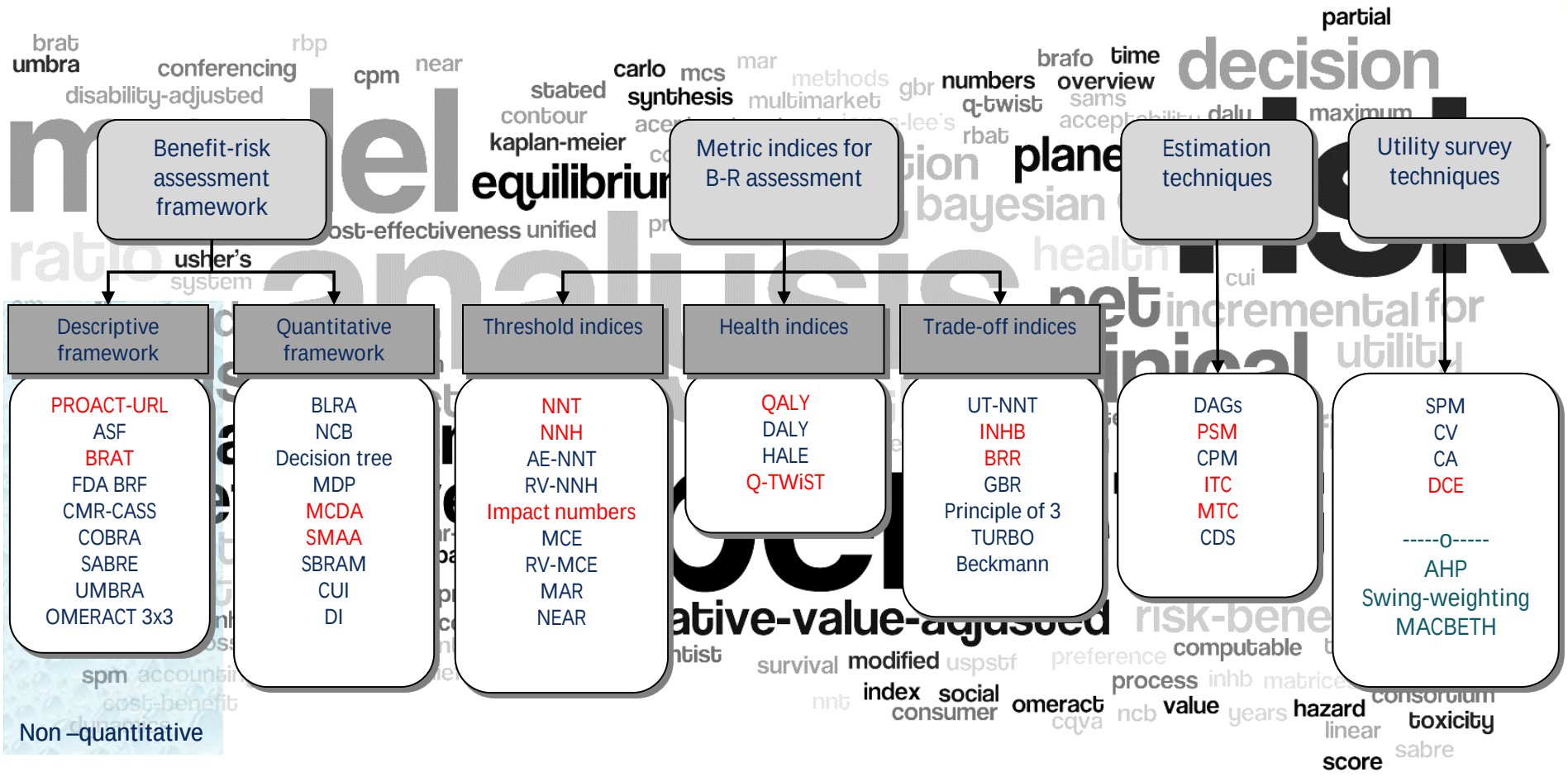
Methodologies available



Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.

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Natalizumab case study

It is an interesting case study because: It is an effective treatment for a serious disease, with a rare but very serious side effect. License suspended in the US but then reintroduced due partly to patient pressure.

Drug of interest	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effect	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved in the US 2005 License suspended in the US 2006 Re-introduced because of patient demand in the US and approved in the EU 2009 CHMP reassessed the PML risk and continued approval

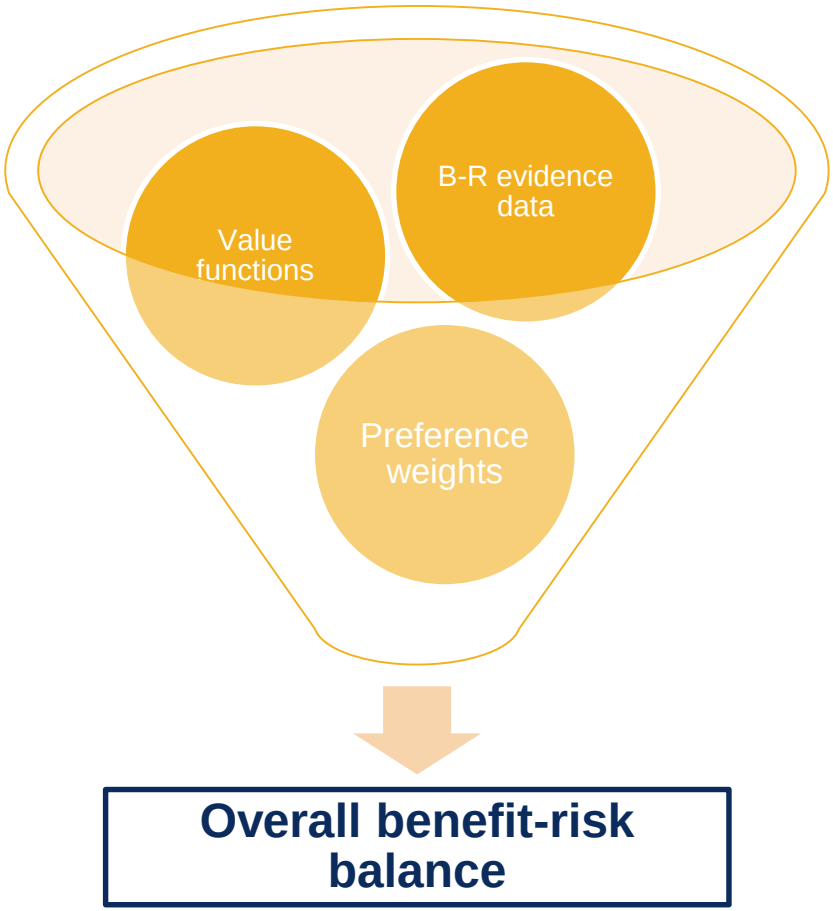
Disclaimers

"The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

Ingredients of MCDA

MCDA has 3 ingredients:



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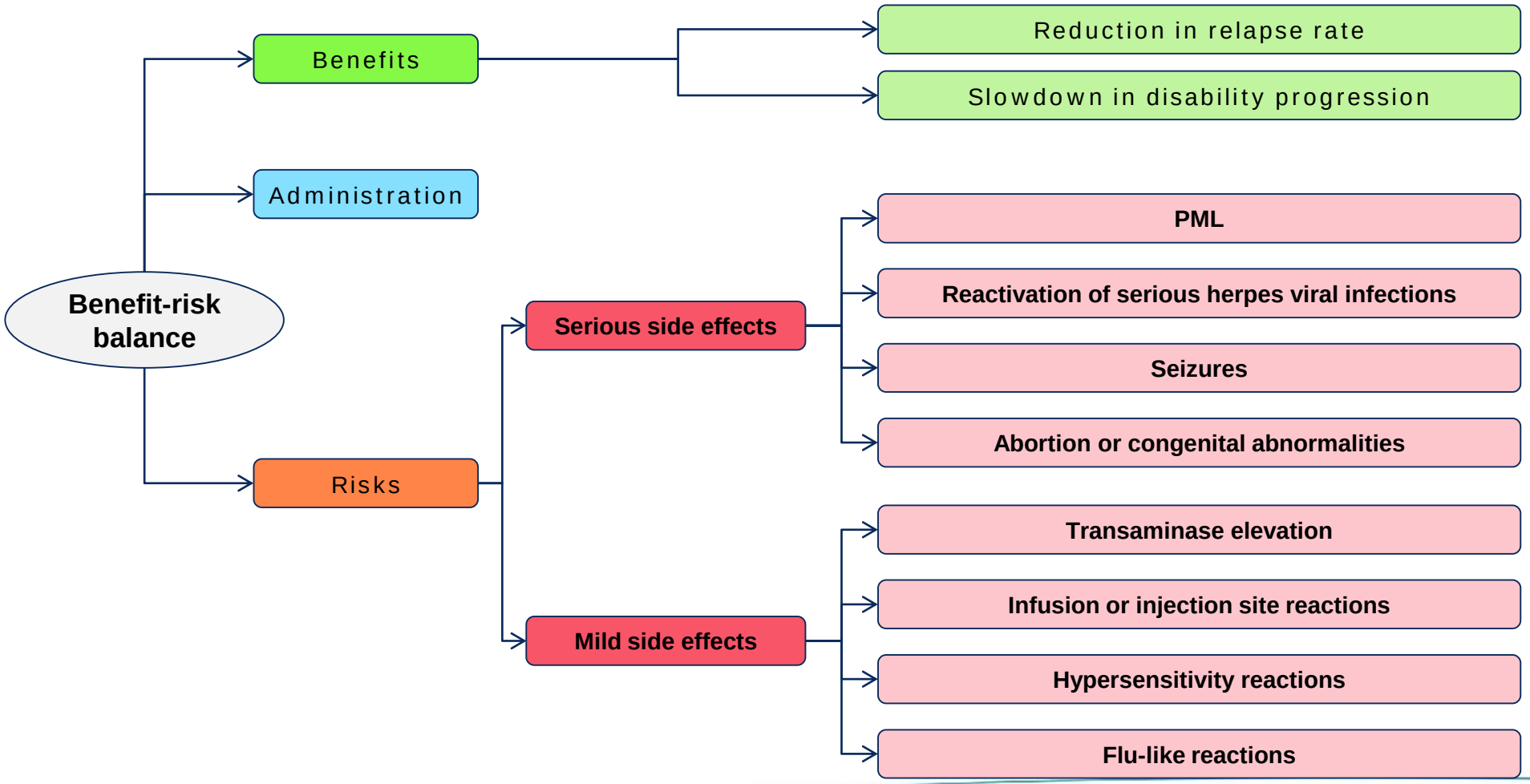
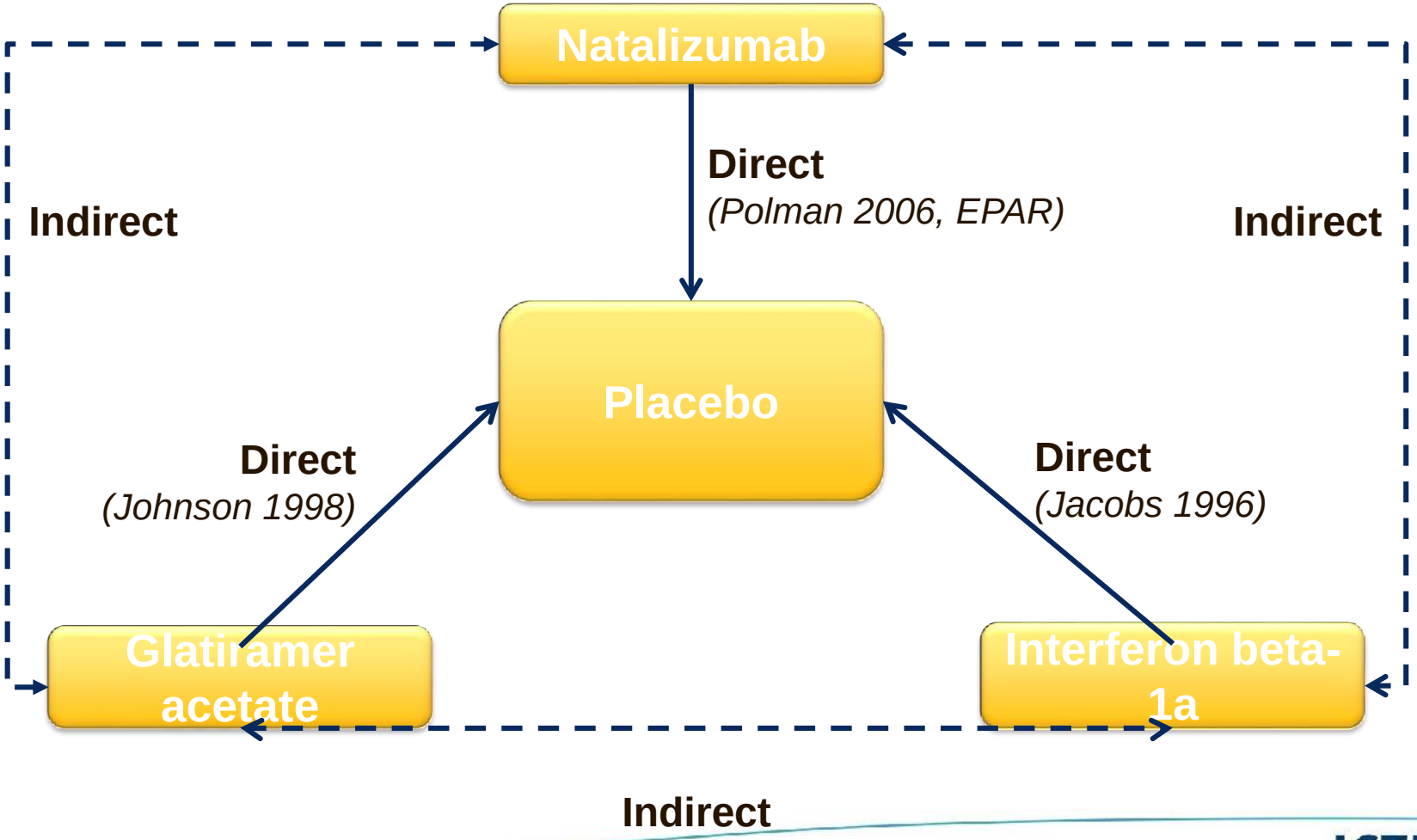
Value tree: Natalizumab case study



An example of MTC network in the natalizumab case study



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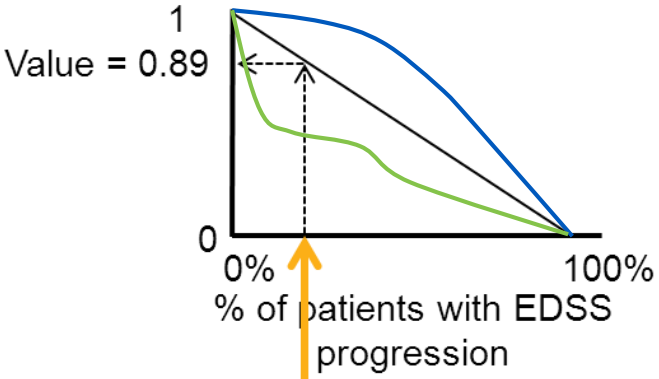
An example of colour-coded tables of data summary

		Outcome	Natalizumab Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts	
Benefits	Convenience Benefits	Convenience (weight 0.6%)	-	-	-	(-, -)
	Medical Benefits	Relapse (weight 3.9%)	280	450	-170	(-, -)
		Disability Progression (weight 5.6%)	110	140	-30	(-, -)
Risks	Infection	Reactivation of serious herpes viral infections (weight 6.7%)	80	70	10	(-26, 45)
		PML (weight 55.9%)	2	0	2	(-, -)
	Liver Toxicity	Transaminases elevation (weight 11.2%)	50	40	10	(-16, 38)
	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	-	(-, -)
	Neurological Disorders	Seizures (weight 5.6%)	0	11	-11	(-23, 0)
	Other	Infusion/Injection reactions (weight 2.8%)	236	312	-76	(-, -)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	608	-209	(-320, -98)

Higher for Drug A

Higher for Comparator

Natalizumab: Weighted utility



Outcome: Disability Progression → **Measure = 11%** → **Value(measure) = 0.89**

Value(measure) = 0.89 and **Elicited Weight = 5%** → **BR Contribution = 0.045**

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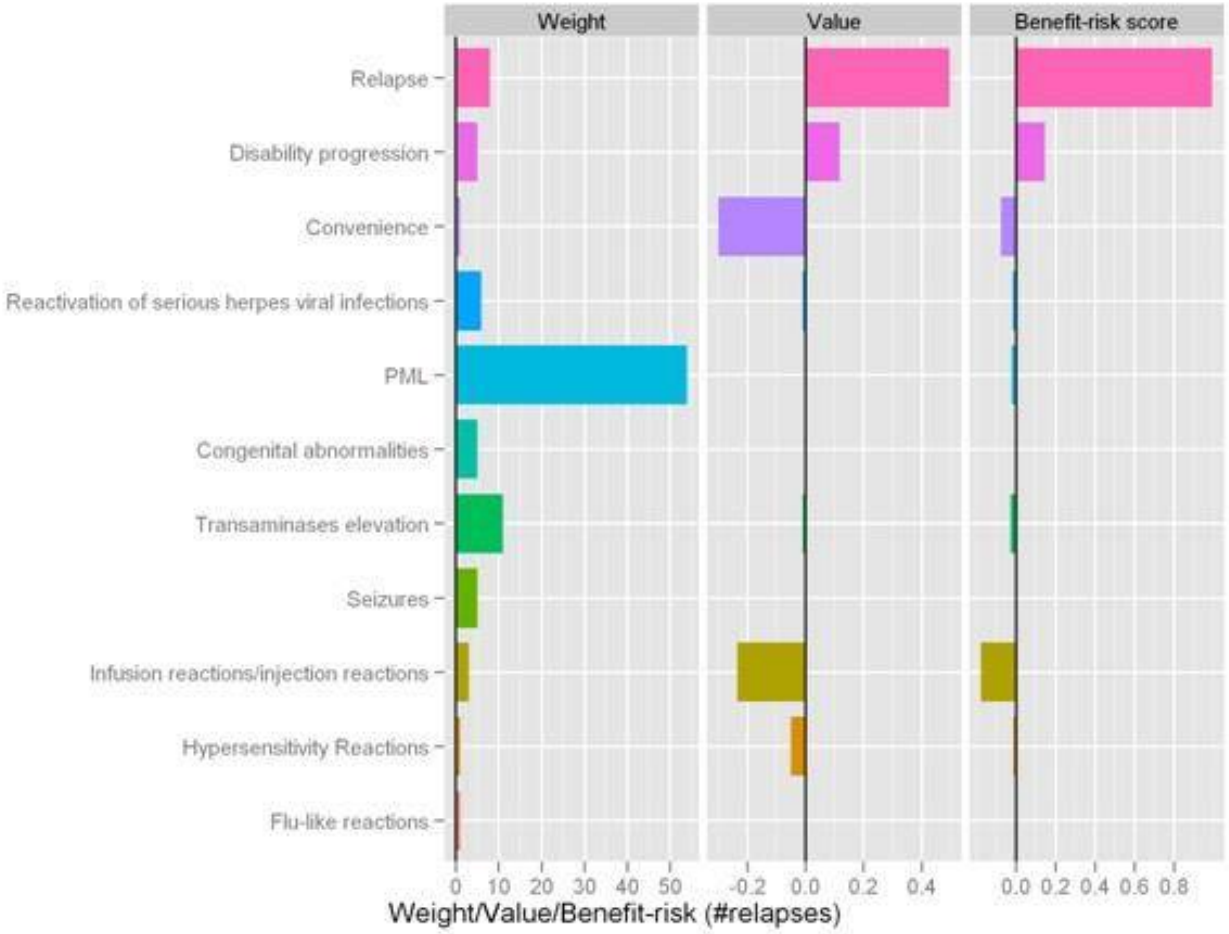
Natalizumab: MCDA weighted utilities analysis

Contribution of each outcome for Natalizumab vs. placebo



- The Benefit-risk is the product of the weight and the value.
- Most of the Benefit-risk contribution is coming from prevention of relapses.
- Infusion site reactions are the worst risk

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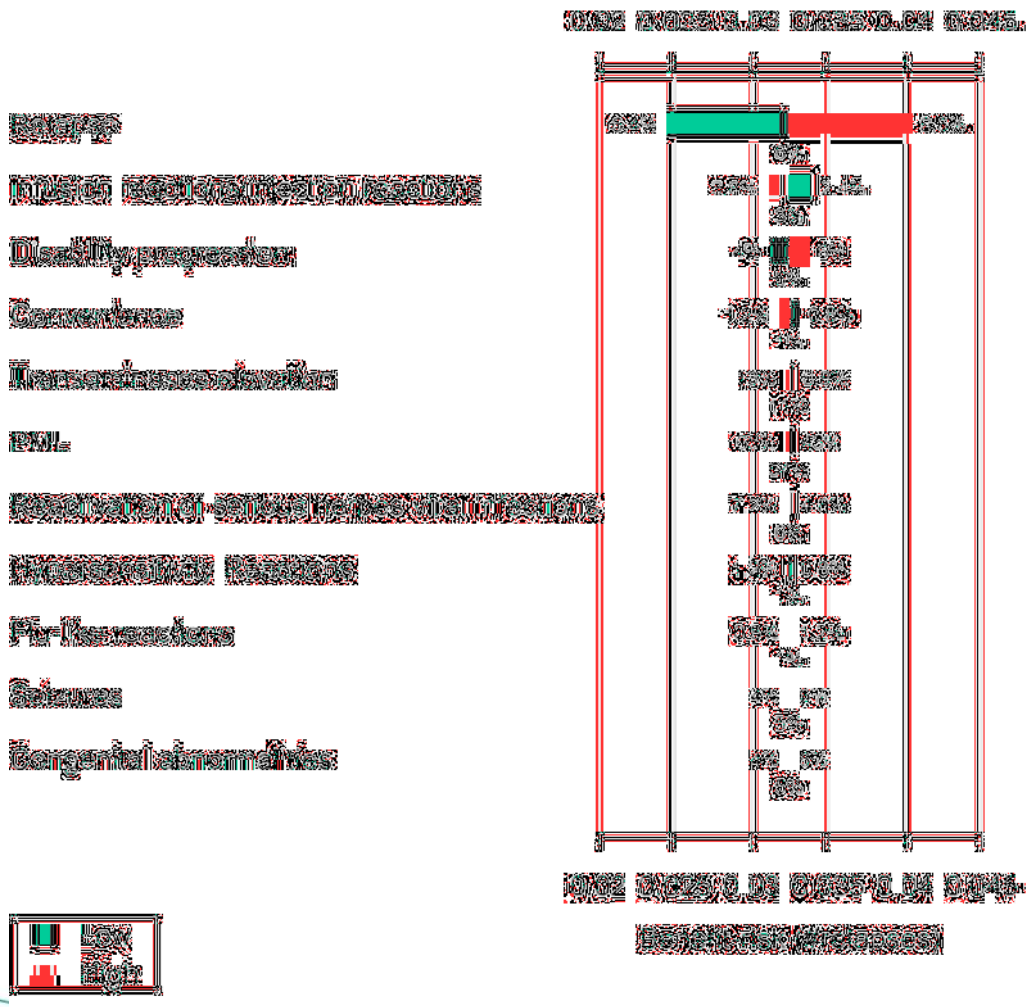
Natalizumab: Uncertainty

Tornado plot for sensitivity to weight: Natalizumab - placebo



- The base case value of the weight for each outcome is shown under each bar.
- The **low values** and **high values** of ±20% change in weight are shown at the ends of the bars.
- The incremental benefit-risk at the base case is the x-axis value at the middle.
- How this changes with each weight is shown by the position of the bar ends.
- From this plot we see that changes in the weight of relapse has the most influence on the benefit-risk score.

tableau SOFTWARE

http://public.tableausoftware.com/views/T_Tornado/T_Tornado

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Decision-making under uncertainty

- Decision-making under uncertainty closely allied with Bayesian statistics for decades, especially in health applications e.g. Raiffa, Schlaiffer, Cornfield, Lindley, Smith AFM, Smith J, Spiegelhalter, Berry, Parmigiani – see Ashby, SiM, 2006 for key references
- Extend uncertainty analysis in a probabilistic model
- Landscape for decisions through entire distributions
- Growing applications but there is still resistance

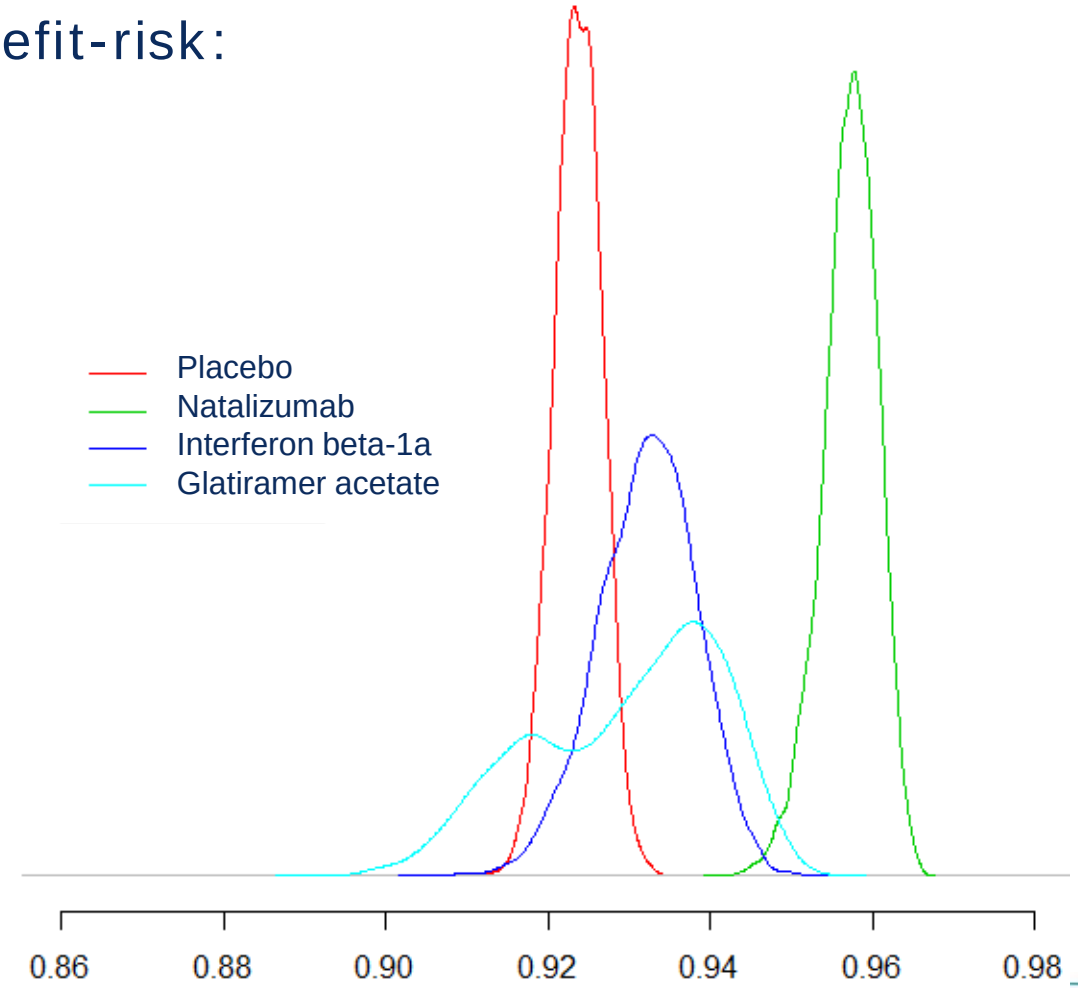
Natalizumab: Probabilistic uncertainty in MCDA

Distribution of overall benefit-risk:

We only allow for clinical parameter uncertainty….

…but the method is easily extendable to value/weight uncertainty

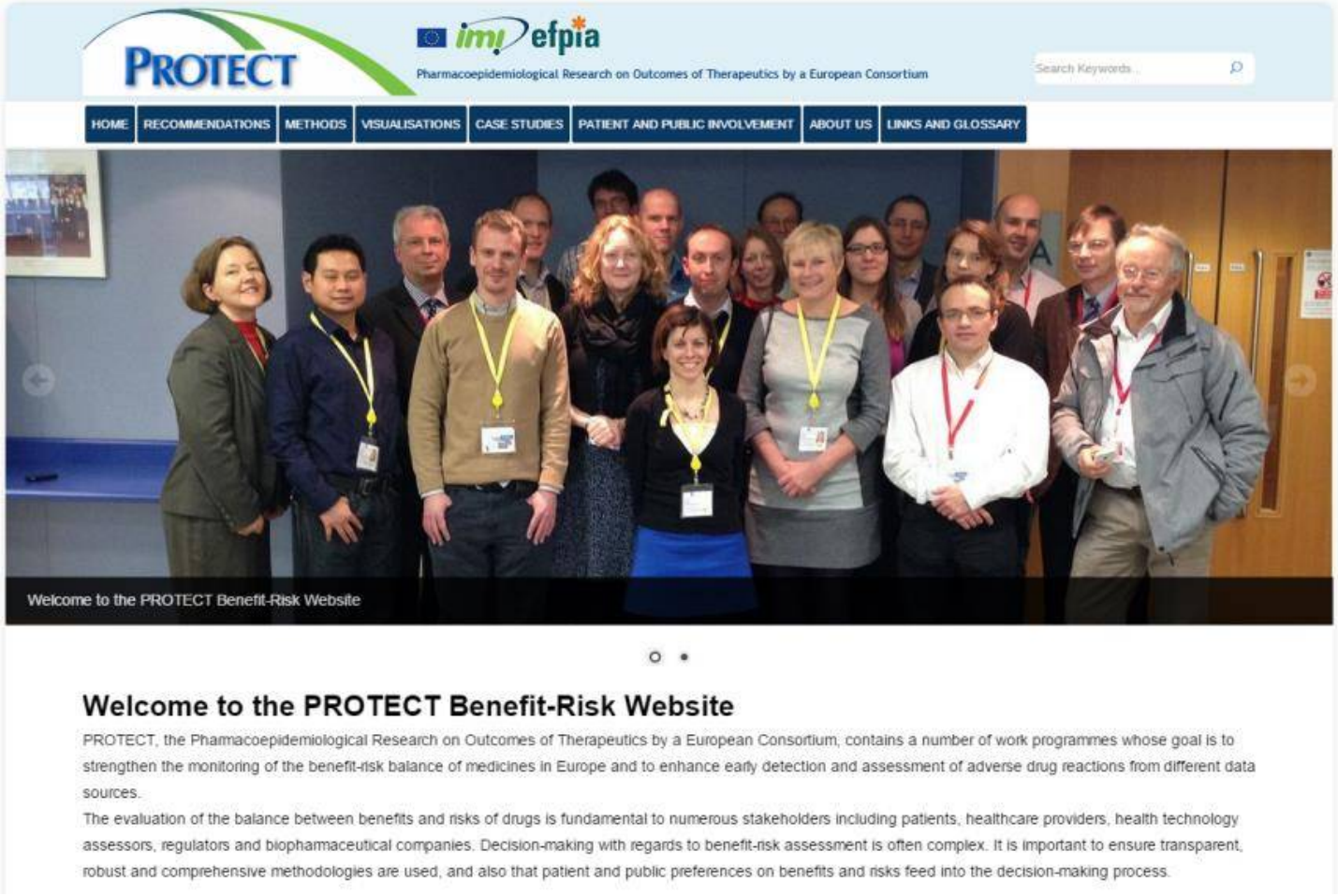
Provides a sense of the statistical significance of differences between treatments



IMI-PROTECT Benefit-Risk Group

- IMI-PROTECT Benefit-Risk Group conducted a:
  - Benefit-Risk Methodology Review,
  - Executed a Visualisation Review in two stages.
  - Applied selected Methodologies and Visualizations to six discrete case studies, conducted in two waves
    - Rimonabant, Telithromycin, Efalizumab, Natalizumab
    - Rosiglitazone, Warfarin (W2 Rimonabant, W2 Natalizumab)
  - Created a Patient and Public Involvement (PPI) Workstream to develop a toolbox for incorporating PPI into medical benefit-risk decision making.

Dissemination and recommendations arising from PROTECT



http://PROTECTBenefitRisk.eu/

Final remarks

- Benefit-risk assessment methodologies support decision-making and are not intended to replace medical expertise.
- Implementation in regulatory settings have begun but there is no harmonisation across organisations
- Future research includes:
  - Vaccines (IMI ADVANCE)
  - Patient and public involvement (IMI PREFER)

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Reflections

- Mathematics- logical; often closed form solutions; abstract and context-independent; precision important
- Statistics- study of uncertainty and variability; finding patterns in data; study design critical; context important but principles transferable
- Population Health- problem solving; context and question important; approximate answers useful; intrinsically multi-disciplinary, but don’t leave your specialist skills at home!
- Making an Impact- answering (and funding) questions that actually need action; engaging fully with colleagues and ways of working in other areas and sectors, often over long periods

Reflections

- “Have nothing in your house that you do not know to be useful, or believe to be beautiful.”
  — William Morris

- “Have nothing in your research portfolio that you do not know to be useful, or believe to be beautiful.”
  — with thanks to William Morris