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Examining GLP-1 Receptor Agonists for CNS Disorders National Academies of Science workshop

September 10th 2024 Washington D.C.

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Conflicts

Advisory Boards	Orion Pharma (migraine therapeutic development)	
Speaker	Nil last 3 years	
Consultant	Medical Doctor, Department of Neurology, University Hospital Birmingham NHS Foundation Trust	
Grant funding (active)	Department of Defence, US (PI 100%) MOD (PI 100%) NIHR HTA (PI 100%) Jules Thorne Award (PI 100%)	£12,734,868 (2023 – 2030) £3,986,882 (2021-2024) £1,517,723 (2021-2027) £1,700,000 (2021-2026)
Other	Vertex Pharmaceuticals, consulting work Previous (2019 – 2022) Director and Chief Scientific Officer (CSO) with Shares at Invex Therapeutics (University spin out company developing GLP-1RA for Idiopathic Intracranial Hypertension)	

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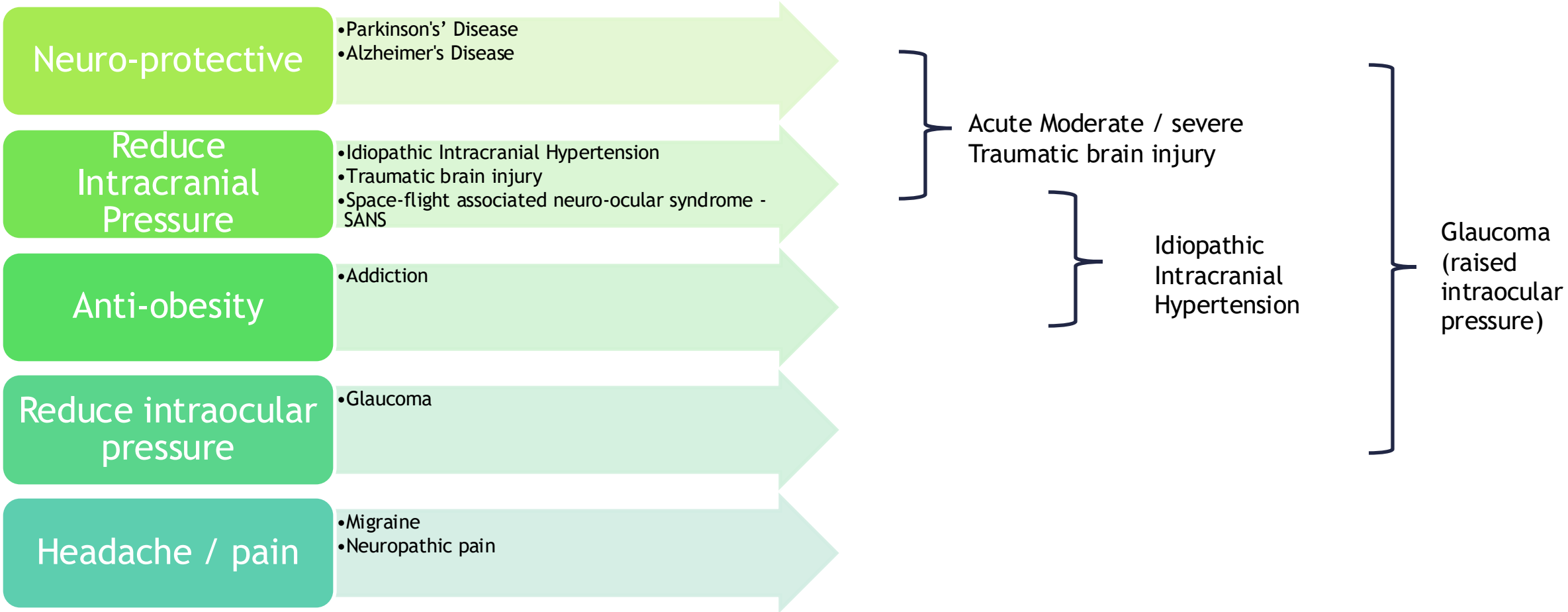
Scoping the effects of GLP-1RA in CNS



Synergistic actions of GLP-1RA → broadens potential clinical utility

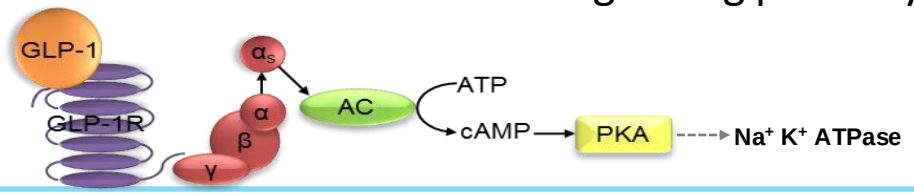
GLP-1 R agonist reduce ICP

GLP-1R expression

- Glucagon like peptide-1 (GLP-1) receptor expression in the choroid plexus

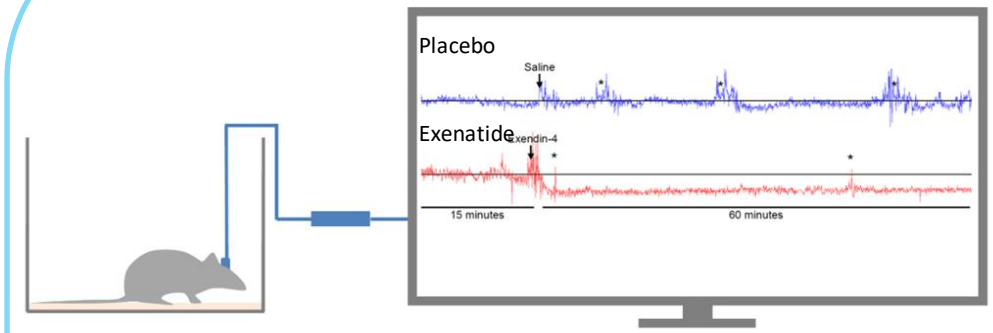
In vitro

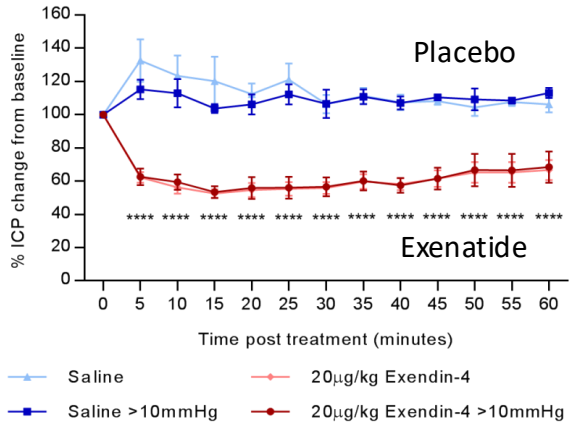
- In vitro work established the signalling pathway



In vivo

- ICP reduction
- Superior to existing drugs in vivo
- Dose response ✓



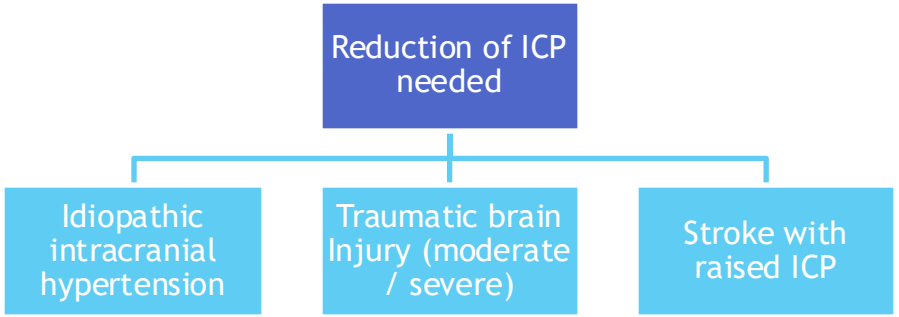


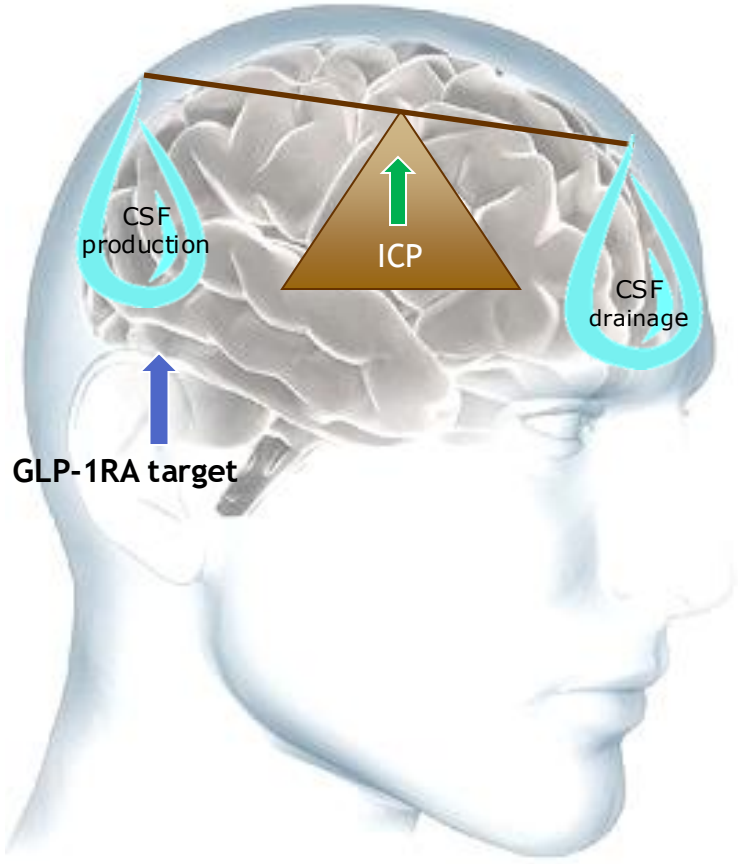
44% drop in ICP with Exenatide

Botfield & Sinclair et al, Sci Trans Med, 2017

GLP-1 to reduce intracranial pressure

- Irrespective of the underlying cause of the raised ICP
  - GLP-1RA reduced ICP





- ICP is dependent on maintaining brain volume → depends on CSF volume, blood volume, tissues volume within the limitations of the rigid skull
- Reducing CSF secretion reduces ICP

Botfield & Sinclair et al, Sci Trans Med, 2017

Idiopathic intracranial hypertension

Likely metabolic aetiology → XS androgens

Women with obesity after puberty → Raised intracranial pressure → Visual loss (25% blindness) + headaches

Pre-clinical data

- GLP-1R expression in choroid plexus epithelium
- GLP-1RA reduce intracranial pressure
- Dose response and half life
- Superior to existing drugs in vivo

Botfield H et al. Sci Trans med 2017

Human data

- Phase 2 Randomised Controlled trial
- Significant reduction in ICP
  - (independent of weight loss)
- Significant reduction headache frequency
- Safe and well tolerated

Mitchell et al. Brain 2023
Krajnc N et al. J Headache Pain 2023

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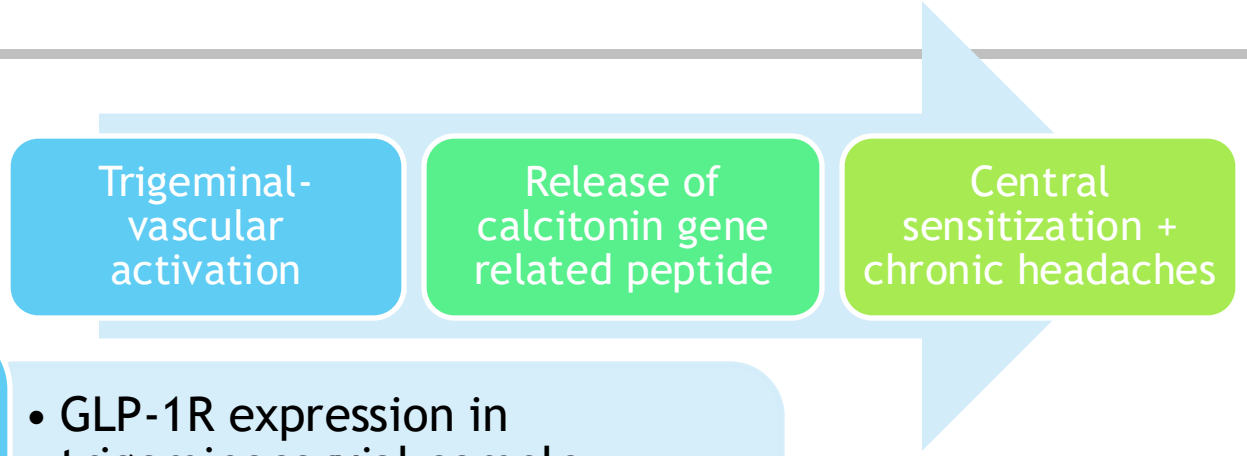
Headache and Migraine

Wealth of data to demonstrate →



Pre-clinical data

- GLP-1R expression in trigeminocervial complex
- GLP-1RA reduced pain by stimulating IL-10 in migraine mouse model

Jing F et al. J headache Pain 2021
Jing F et al. Neurosci Lett 2023
****Halloum W et al. J Headcahe Pian 2024 (reviev*

Human data

- Open label migraine patients with obesity (n=26), reduced headache frequency not BMI.

Braca S et al Migraine Trust Internation Symposiun conference abstract Sept 2024

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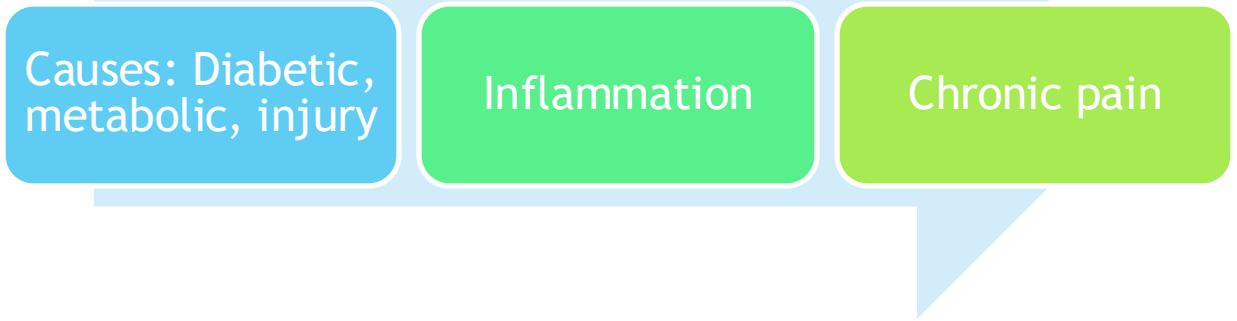
Neuropathic pain – (chronic)

Wealth of data to demonstrate →



Pre-clinical data

- GLP-1R agonists activate GLP-1R on microglia in spinal dorsal horn
- Increased IL-10 and reduced inflammatory markers
- GLP-1RA reduced neuropathic pain and pain signalling in mice models
- GLP-1RA mediates ß-endorphins and μ receptors in neurones

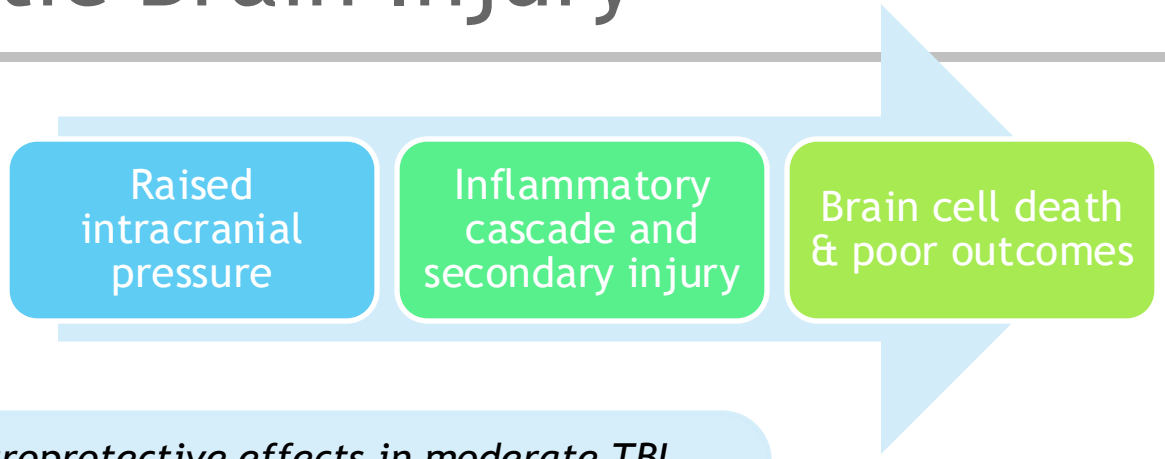
Human data

- Nil.....

Gong N et al. NeuroSci 2014
Zhong K et al Neurol Sci Neurophysiol 2024
Ma L et al. NeuroPlast 2021
Xu M et al. Br J Pharmacol 2017
****Halloum W et al. J Headcahe Pian 2024 (review)*

Traumatic Brain Injury

Wealth of data to demonstrate →



Pre-clinical data

- *Neuroprotective effects in moderate TBI*
- GLP-1RA improved function outcomes in rodents
  - Attenuated inflammation
  - Improved cognitive recovery

Human data

- Nil……

Zang J. et al. Int Immunopharmacol 2020
Chen H et al. Sci Rep 2018
Eakin K et al. PLOS one 2013
Rahmany L et al. Age (dordr) 2012
Tweedie D et al. Exp neurol 2013
Li Y et al. J Neurochem 2010

Severe TBI is Akin to ischaemic stroke and subarachnoid haemorrhage.

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Glaucoma

Wealth of data to demonstrate →

Raised intraocular pressure → Retinal ganglion cell death → Optic nerve atrophy and visual loss

Pre-clinical data

- GLP-1RA actions in the retinal ganglion cells of optic nerve
  - Anti-inflammatory
  - Anti-oxidative stress
  - Reduced apoptosis

Sterling J et al. Cell Rep 2020
Lawrence E et al. Front Cell NeuroSci 2023

Human data

- Retrospective case review (n=1961 + 1737) demonstrated lower risk on glaucoma in those on GLP-1RA
- Lower IOP after glaucoma surgery (retrospective cohort study)

Sterling J et al. Br J Ophthalmology 2023
Niazi et al. Ophthalmology 2024
Hallaj et al. MedRxix pre print 2024

Opportunities - GLP-1R agonist in the brain

Diabetes and Obesity "tip of the iceberg"

Anti-obesity drug

Type 2 Diabetes mellitus

Raised Intracranial pressure

Idiopathic intracranial hypertension
Traumatic brain injury

Headache & migraine

'Neuropathic pain'

Raised Intraocular pressure (glaucoma)

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Opportunities for personalised medicine

Multi-morbid patients

e.g. obesity, diabetes, cardiovascular disease, migraine +/- glaucoma

Consider issues:
Drug compliance, side effects, long term safety, cost

Multi-modal actions of GLP-1RA

Taylor drug effects to specific patient sub-groups depending on their co-morbidities

Personalised medicine approach

Who will benefit most?
Is it cost effective?

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Future

Translation to humans

- Need randomised controlled trials

Effect comparability by gender

- Important
  - Many diseases have gender bias
- A gap in knowledge

Evaluate utility of GLP-1RA to reduce analgesic overuse and opiate use in pain / migraine

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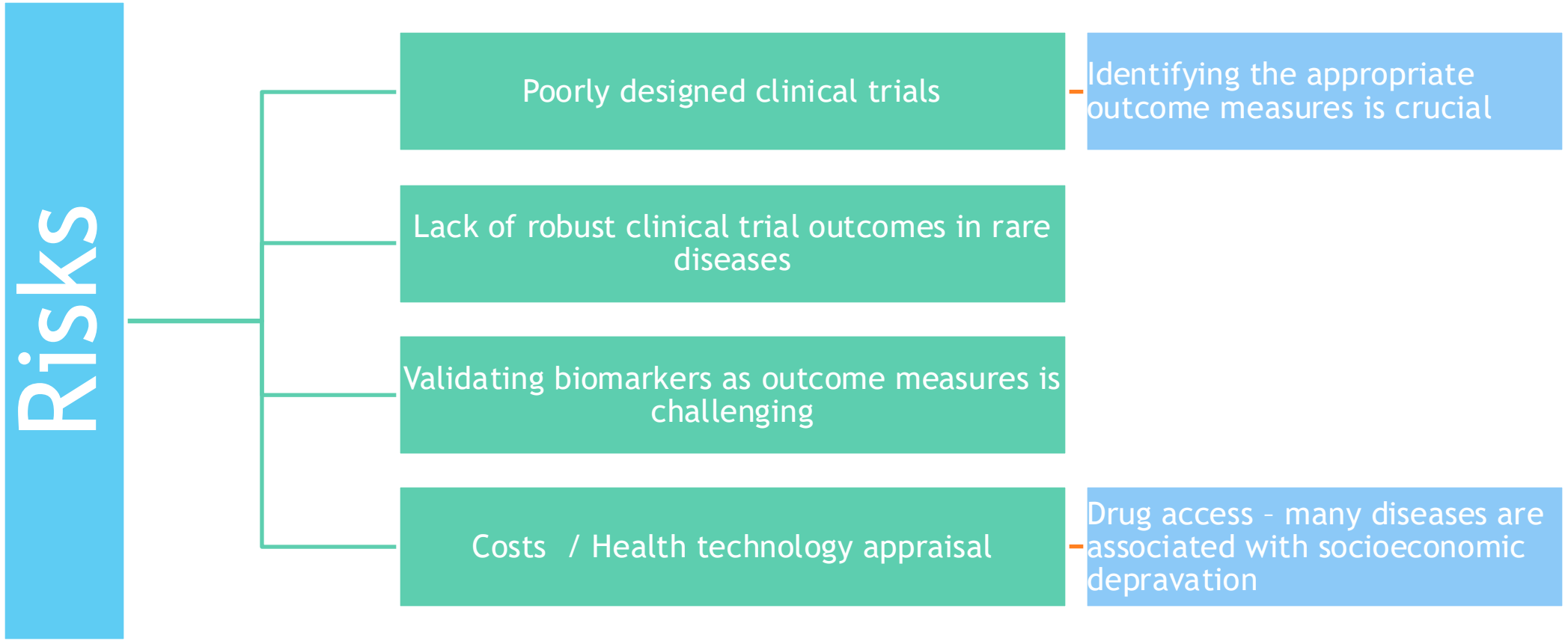
Risks



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Questions