Institute and Faculty of Actuaries

IFoA Life Conference

GLP-1 Receptor Agonists and the Future of Mortality:

What Actuaries Need to Know

GLP-1 & GIP Receptor Agonists

Mechanism, Clinical Impact, and Future Developments

Source: https://species.wikimedia.org/wiki/Heloderma_suspectum

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Background

Key learnings from this session

1. How GLP-1 & GIP receptor agonists work and why they are important

2. The latest clinical findings and their broader health benefits

3. The risks, challenges, and future considerations

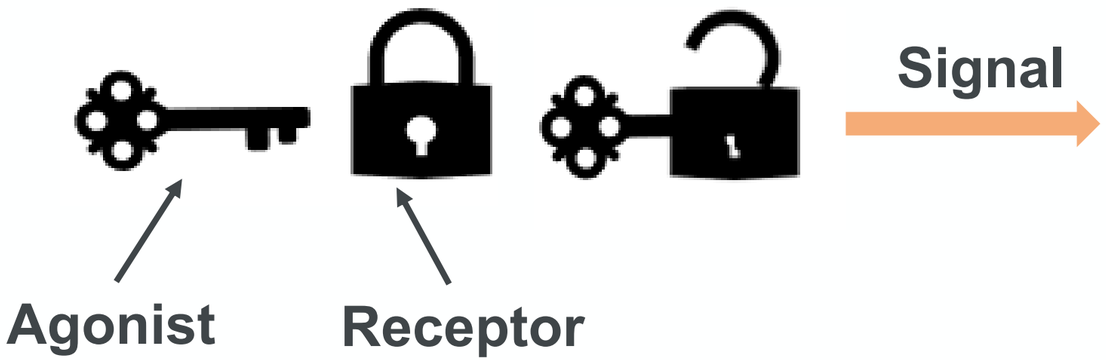
What is a receptor agonist?

In the gut, hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), signal the body to release insulin, slow digestion, and promote feelings of fullness.

A GLP-1 or GIP receptor agonist is a drug that mimics the action of these gut hormones, activating their receptors to enhance insulin release only when blood glucose levels are high, while also slowing digestion and reducing appetite.

It’s not a stimulant; it’s a copy of a natural signal.

Think of a receptor as a lock on a cell. An agonist is a key that fits the lock and opens it, triggering the same response the body’s natural messenger would.



Main Effects

It's not just "GLP-1 + GIP = 2x effect"

Dual agonism can be complementary

Bone

↑ Bone Formation

Brain

↑ Memory

↑ Memory

↓ Food Intake

GIP

↑ Glucagon

↑ Insulin

↓ B-cell Apoptosis

↑ B-cell Proliferation

Pancreas

↓ Glucagon

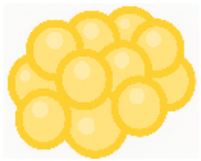
↑ Insulin

↓ B-cell Apoptosis

↑ B-cell Proliferation

GLP-1

↑ Fat Accumulation



Fat tissue

↓ Gastric Acid Secretion

GI Tract

↓ Gastric Emptying

↑ Cardioprotection

↑ Cardiac Output

Heart

Figure adapted from: Seino et al, GIP and GLP-1, the two incretin hormones: Similarities and differences J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00022.x, 2010

Approved GLP-1 and GIP Receptor Agonists

Liraglutide (Victoza, Saxenda)

Daily injection

Heart benefits

Semaglutide (Ozempic, Wegovy)

Weekly injection or oral

Most effective single GLP-1

Tirzepatide (Mounjaro, Zepbound)

Weekly Dual GLP-1/GIP, superior weight loss

Approvals

Sources: FDA (USA); EMA (EU/EEA); MHRA and NICE (UK); TGA and PBAC (Australia); Medsafe and Pharmac (New Zealand); MFDS and HIRA (South Korea); Health Canada and CADTH (Canada).

Drug (Brand)*	Indication beyond weight loss	Country & date of approval
Semaglutide (Wegovy)	**MACE** in adults with **CVD** and/or **overweight/obesity**, with/without **diabetes**	**USA** March 2024 **European Union / EEA July** 2024 **UK** July 2024 **Australia** December 2024 **New Zealand** 2025 **South Korea** August 2024
	Non-fatal **MI** risk reduction in adults with **CVD** and BMI ≥27 kg/m²	**Canada** November 2024
Semaglutide (Ozempic)	**Type 2 diabetes mellitus**	**USA** December 2017 **European Union / EEA** February 2018 **UK** January 2019
	Noncirrhotic **MASH** (F2–F3)	**USA** August 2025
	Kidney disease and **CVD** in adults with **T2D + CKD**	**European Union / EEA** 2025 **Australia** August 2025, **Canada** August 2025
Tirzepatide (Zepbound)	Moderate-to-severe obstructive **sleep apnoea** in adults with **obesity**	**USA** December 2024 **European Union / EEA** December 2024 **Australia** June 2025 **South Korea** August 2025

*Even though Wegovy and Ozempic contain the same active ingredient, they are approved for different uses, have different doses and treat different age groups. The same goes for Zepbound and Mounjaro.

MACE = Major adverse cardiovascular events. Refers to a set of serious and potentially life-threatening conditions that affect the heart and blood vessels. These events include death, non-fatal myocardial infarction (heart attack), and revascularisation (a procedure to restore blood flow to the heart). CKD = chronic kidney disease CVD = cardiovascular disease MASH = noncirrhotic metabolic dysfunction-associated steatohepatitis T2D = type 2 diabetes

Approvals

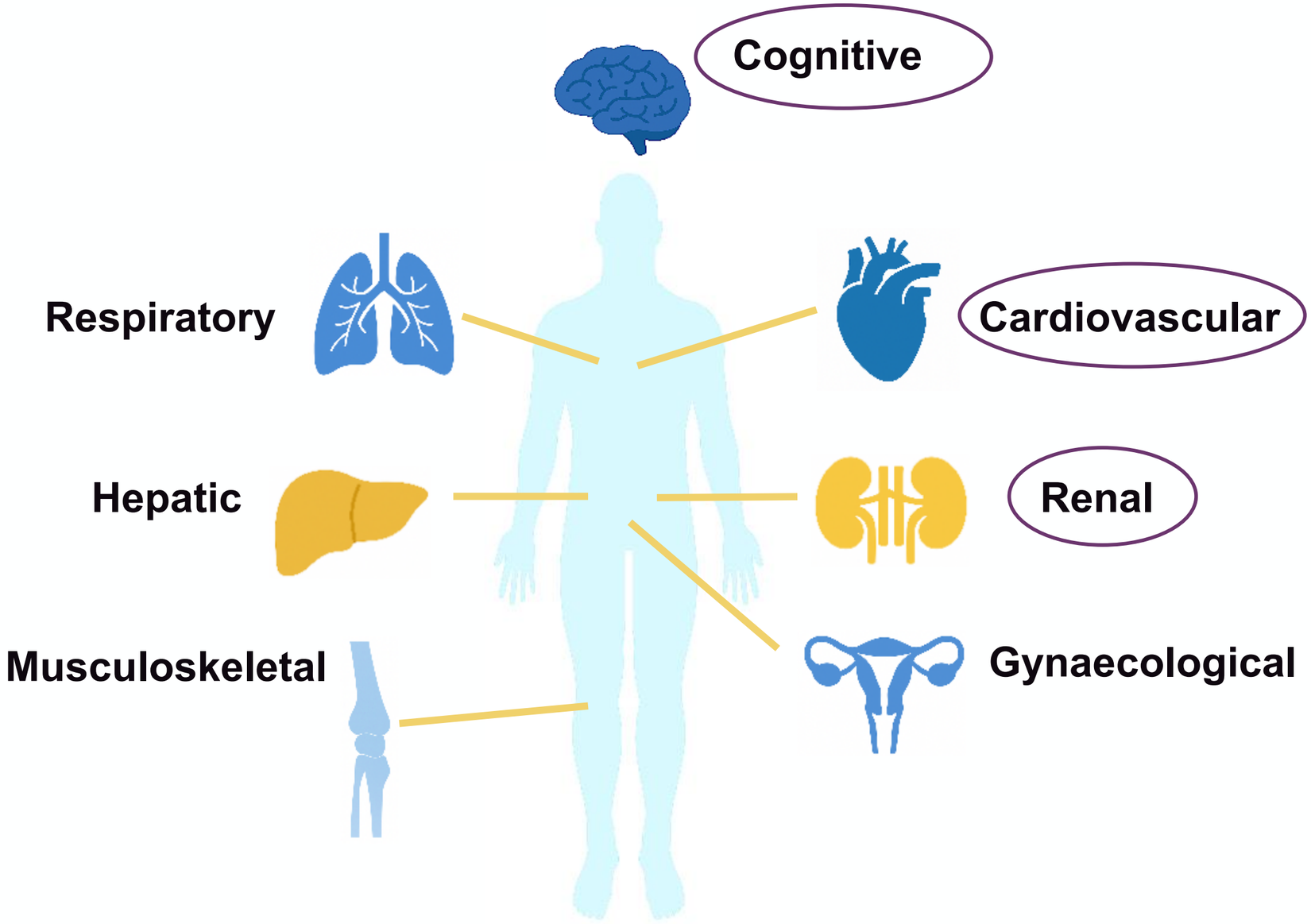
Not approved beyond weight loss

Japan

Singapore

China

Potential benefits beyond weight management



Multiple studies + meta-analyses

Cardiovascular – cardiometabolic protection

11% heart failure risk reduction

9% heart attack risk reduction

7-14% stroke risk reduction

22% cardiac arrest risk reduction

20% lower risk of major cardiovascular events

Cognitive protection

5% overall Neurocognitive disorders risk reduction

8% dementia risk reduction

12% Alzheimer's disease risk reduction

10% seizures risk reduction

Psychiatric/behavioural outcomes

10% suicidal ideation/attempt/self-harm risk reduction

18% schizophrenia & other psychotic disorders risk reduction

19% bulimia risk reduction

Renal protection

12% acute kidney injury risk reduction

3% lower incidence of chronic kidney disease

Risks & Considerations

- ⚠ **Potential Risks:**
- Gastrointestinal side effects (nausea, vomiting)
- Increased risk of pancreatitis
- Risk of blood pressure drops
- Increased risk of renal inflammation
- Increased risk of some musculoskeletal conditions

- ⚠ **Who Needs Caution:**
- Patients prone to kidney stones
- Those with severe GI issues or joint pain

Anti-ageing therapeutic?

May influence key hallmarks of ageing:

- Cellular senescence
- Chronic inflammation ("inflammaging")
- Metabolic dysfunction

Emerging evidence:

- Attenuation of low-grade inflammation seen in ageing
  - Reductions in markers of:
    - ✓Cellular senescence
    - ✓Oxidative stress
    - ✓Suggests systemic impact beyond glycaemic control

Summary

GLP-1 & GIP receptor agonists may redefine **obesity** & chronic disease management, compelling benefits with meaningful uncertainties (durability, adherence, access)

Strong **cardiovascular, metabolic**, **renal** and **neuroprotective** benefits, **anti-ageing potential**

Adverse **side-effects** must be considered

Cost and **access** remain major **barriers**

Modelling potential impact

How can we model an anti-ageing scenario?

Estimating Future Biological Age

Ageing Rate Reduction
- Gerotherapeutic Ageing Rate Reduction from rodent studies

Human Disease-specific Ageing Rate
- Currently observed disease-specific mortality rates by age/gender
- Proportion of disease likely to be affected (ageing relatedness)
- Evidence of link to hallmark of aging

Take-up Transition
- Delay due to drug development pipeline
- Take-up transition

Access & Compliance
- Access to healthcare
- Compliance with intervention

Ageing-Related Clinical Trials with GLP-1 RAs

Assumptions

- Base ageing rate reduction factor (ARRF) the same as that for mToR (61%).[1,2]
- The ARRF is adjusted by real-world trajectories for completion of R&D, licensing, HTA, accessibility and compliance.
- Biological age assigned to a cause of death linked to an affected hallmark of ageing is adjusted by the ARRF weighted by the ‘ageing relatedness’ of the condition.[3] All others age normally.
- The sum of the cause specific mortality rates for the given biological age is summed.

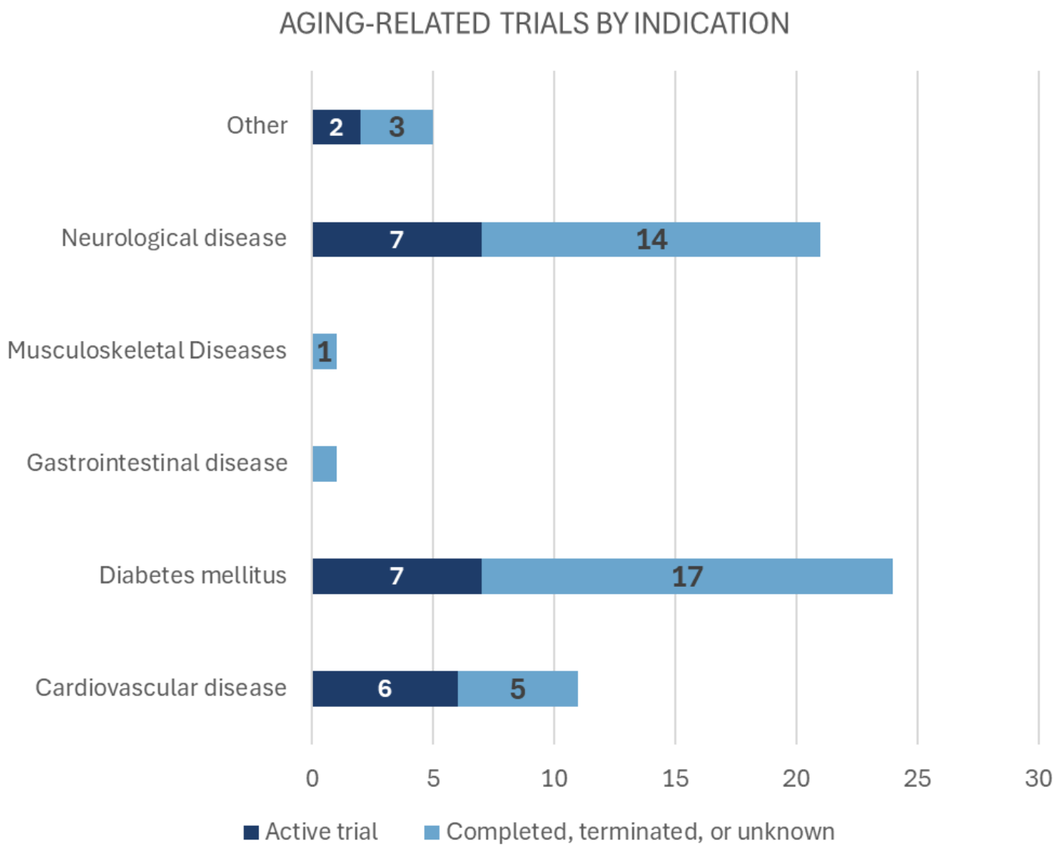
1. Crystallise Geroscience Focus issue 1. 2024. Geroscience Spotlight - Rapamycin (mTOR inhibitors).
2. Mannick, J.B., Lamming, D.W. Targeting the biology of aging with mTOR inhibitors. Nat Aging 3, 642–660 (2023). https://doi.org/10.1038/s43587-023-00416-y
2. Huang J, Kwok AJ, Li JCY, Chiu CLH, Ip BY, Tung LY, et al. Functional and multi-omic aging rejuvenation with GLP-1R agonism [Internet]. Systems Biology; 2024

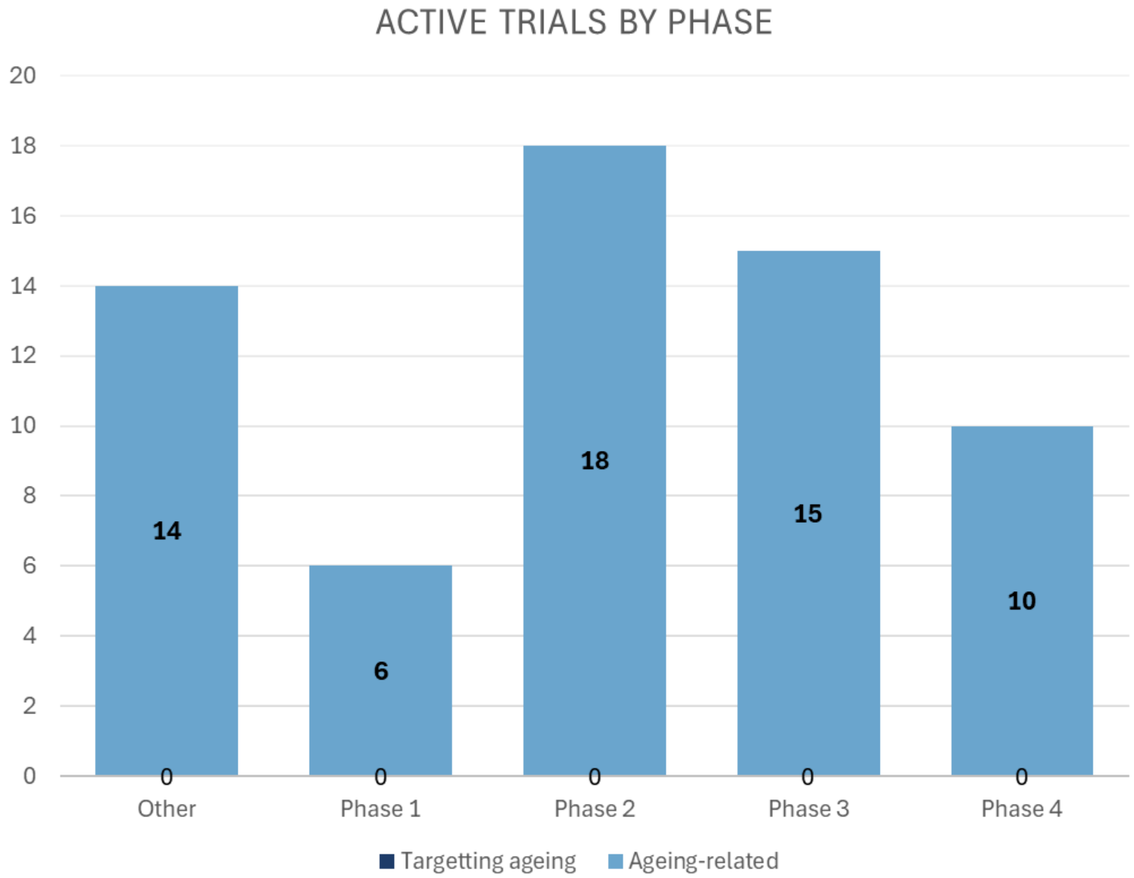
Step 1. Map CoD to hallmarks of ageing affected

Cause of Death	Modulate using Hallmark-ARD Mapping?	Aging Relatedness		Genomic instability	Telomere attrition	Epigenetic alterations	Loss of proteostasis	Disabled macroautophagy	Deregulated nutrient sensing	Mitochondrial dysfunction	Cellular senescence	Stem cell exhaustion	Altered intracellular communication	Chronic inflammation	Dysbiosis
				4a. What hallmarks do the interventions target?											
Targetted hallmarks ->	TRUE	TRUE		0	0	0	0	1	1	1	1	0	0	1	0
				4b. Does sufficient evidence exists for specific disease category? 1=Yes, =No. tagged in top 50 of Kuan Study.											
Infections and Parasites	TRUE	0.97		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	FALSE
Cancers	TRUE	0.97		TRUE	TRUE	TRUE	TRUE	TRUE	FALSE	FALSE	TRUE	TRUE	TRUE	TRUE	TRUE
Blood Disorders	FALSE	0.69		FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE
Endocrine and metabolic	TRUE	0.80		FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	TRUE	TRUE	TRUE
Cardiovascular Disease	TRUE	0.86		FALSE	TRUE	FALSE	FALSE	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE
Mental and behavioural	TRUE	0.99		FALSE	TRUE	FALSE	TRUE	TRUE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE
Nervous System	TRUE	0.84		FALSE	FALSE	FALSE	TRUE	TRUE	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	FALSE
Eye Diseases	TRUE	0.35		FALSE	FALSE	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Ear Diseases	FALSE	0.93		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Respiratory Diseases	TRUE	0.94		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	TRUE	TRUE	TRUE
Digestive System	TRUE	0.70		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE
Skin Diseases	FALSE	0.62		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Musculoskeletal	TRUE	0.81		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	TRUE	TRUE
Genitourinary	TRUE	0.90		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	TRUE	TRUE
Pregnancy & childbirth	TRUE	0.01		FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Newborn Conditions	TRUE	0.13		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE
Congenital malformations, deformations and	FALSE	0.00		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Symptoms not elsewhere classified (incl. Old	FALSE	0.50		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
External causes	FALSE	0.00		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Codes for special purposes	FALSE	0.00		FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE

Screenshot of the cause of death to hallmark of ageing mapping in the Crystallise ageing model.

Ageing-Related Clinical Trials with GLP-1 RAs





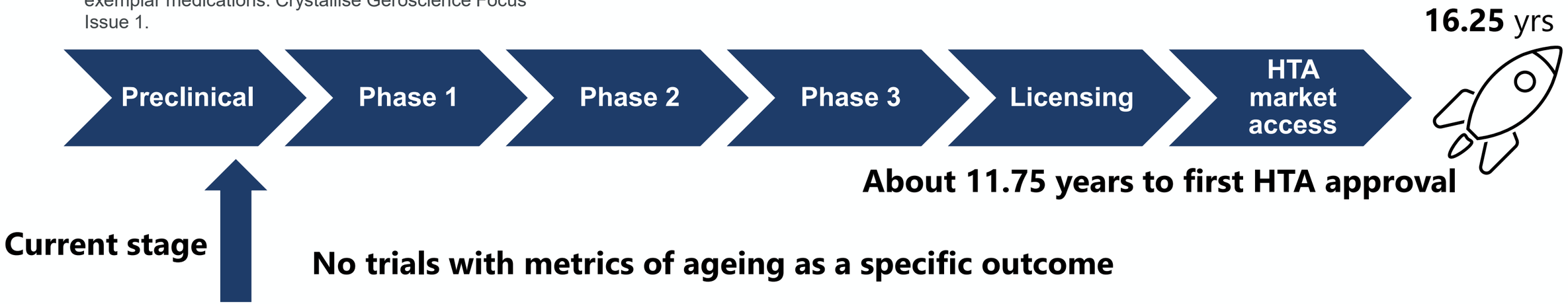
* Other: Completed, terminated, or status unknown

From www.clinicaltrials.gov

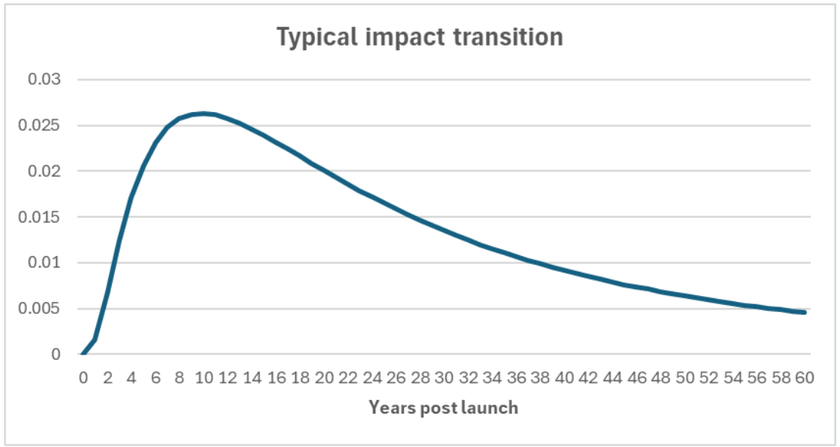
Step 2: Calculate trajectories of impact

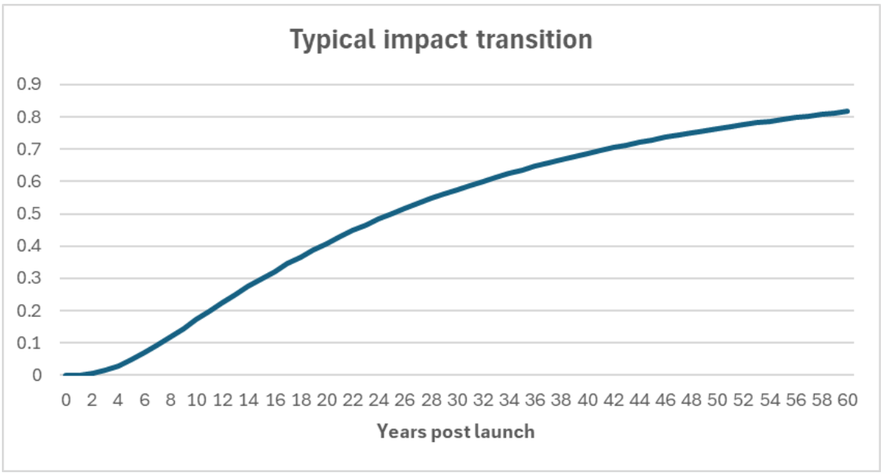
- Pipeline database – 0 trials of mTOR inhibitors specifically targeting aging.
- Start of phase 1 in a typical drug development timeline would be 4.5 years into a 16.25 year development cycle.
- **Assuming a successful R&D development cycle with phase 1 trials starting now, then it would typically take 11-12 years for HTA approval to be achieved.**

Estimated based on times to approximate first impact on mortality and peak historical mortality benefit of the exemplar medications. Crystallise Geroscience Focus Issue 1.



Step 2: Timing (improved transition model)





Timing	Delay	Transition (Mu)	Transition (sd)
Slow	15	30	0.3
Typical	15	20	0.3
Fast	15	12	0.3

Estimated based on times to approximate first impact on mortality and peak historical mortality benefit of the exemplar medications. Crystallise Geroscience Focus Issue 1.

Based on historical experience with:

- Statins
- Aspirin
- Tamoxifen
- Monoclonal antibodies

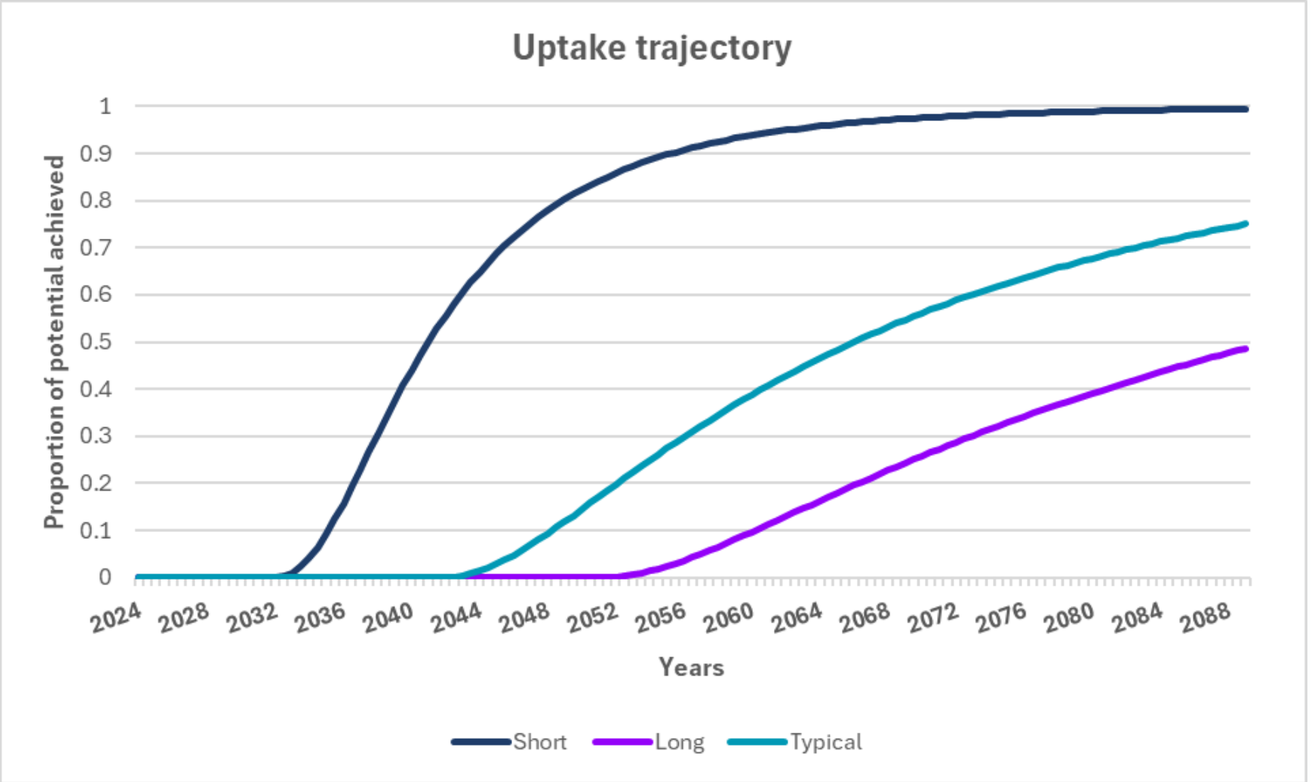
Step 2: Calculate trajectories of impact

In years	Short	Long	Typical
Pre-Clinical	3	6	4.5
Phase 1 trials	0.5	4.1	2.3
Phase 2 trials	1	6.2	3.6
Phase 3 trials	1	5.6	3.3
Time to licensing	0.5	2.1	1.3
Time to HTA approval	0.5	2	1.25

Based on data from:
https://www.biostock.se/en/2023/01/drug-development-the-four-phases/
https://www.n-side.com/en/insights/whats-the-average-time-to-bring-a-drug-to-market-in-2022/

Compliance	Adjustment Factor
Low	0.4
Typical	0.65
High	0.9
No Adjustment	1

Access	Adjustment Factor
Low	0.8
Typical	0.85
High	0.95
No Adjustment	1



From the Crystallise ageing model based on historical milestones for a set of innovative, high impact medications (statins, aspirin, monoclonal antibodies, GLP-1 agonists).

Adjustment factors estimated based on a review of the literature on compliance, and analysis of trends in waiting times and response times in the NHS. Crystallise Geroscience Focus issue 1.

Step 3. Calculate biological age for each CoD

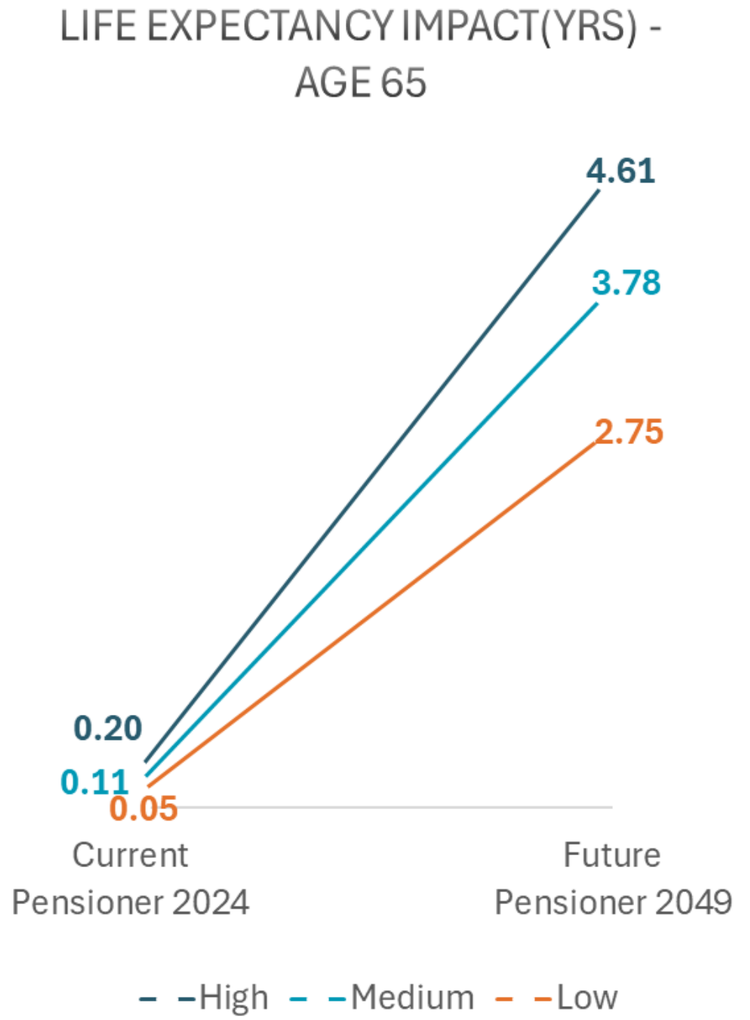
Chronological Age	Time	Infections and Parasites	Cancers	Blood Disorders	Endocrine and metaboli	Cardiovascular Disease	Mental and behavioural	Nervous System	Eye Diseases	Ear Diseases	Respiratory Diseases	Digestive System	Skin Diseases	Musculoskeletal	Geni
65.00	0	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65.00	65
66.00	1	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66
67.00	2	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67.00	67
68.00	3	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68.00	68
69.00	4	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69.00	69
70.00	5	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70
71.00	6	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71.00	71
72.00	7	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72.00	72
73.00	8	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73.00	73
74.00	9	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74.00	74
75.00	10	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75
76.00	11	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76.00	76
77.00	12	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77.00	77
78.00	13	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78.00	78
79.00	14	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79.00	79
80.00	15	79.99	79.99	80.00	79.99	79.99	79.99	79.99	80.00	80.00	79.99	80.00	80.00	79.99	79
81.00	16	80.98	80.98	81.00	80.98	80.98	80.98	80.98	80.99	81.00	80.98	80.99	81.00	80.98	80
82.00	17	81.96	81.96	82.00	81.97	81.97	81.96	81.97	81.99	82.00	81.96	81.97	82.00	81.97	81
83.00	18	82.93	82.93	83.00	82.94	82.94	82.93	82.94	82.98	83.00	82.94	82.95	83.00	82.94	82
84.00	19	83.89	83.89	84.00	83.91	83.91	83.89	83.91	83.96	84.00	83.90	83.92	84.00	83.91	83
85.00	20	84.85	84.85	85.00	84.87	84.86	84.84	84.87	84.94	85.00	84.85	84.89	85.00	84.87	84
86.00	21	85.79	85.79	86.00	85.82	85.81	85.78	85.82	85.92	86.00	85.79	85.85	86.00	85.82	85

Screenshot of a heatmap of biological age versus chronological age by cause of death in the Crystallise ageing model. This yields an adjusted human ARR of about 19%.

Results for GLP-1

- Animal model ARR: 39%
  Effective human ARR: 19%
- Potential time to take-up modelled as range and could take up to 26 years for first approval
- Access and Compliance is captured as a range based on historic interventions.

- **Impact:**
  - Gerotherapeutics are generally not a significant concern for current pensioner population
  - Future pensioner populations will see the benefits, but this is still highly uncertain
  - What about the current growing ‘lifestyle’ use?



Q&A

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