Crystallise
Insights

GEROSCIENCE FOCUS

A report produced by Crystallise Ltd

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Contents

This is the first edition of the Geroscience Focus Report.

Contributors

This report has been developed by Crystallise Limited with the help of its steering committee:

- **Uli Stengele**, FSA
- **Fred Slater**, FSA
- **Richard Faragher**, Professor of Biological Gerontology at the University of Brighton
- **Joseph Lu**, FIA

The Longevity Science Panel (https://www.longevitypanel.co.uk/members/), advised on the publication.

The Crystallise team members contributing to this issue were:
Andrea Bertuzzi
Jay Bilimoria
Ashley Campbell
Nicky Draper
Christianah Edema
Eleanor King
William Letton
Chris Martin
Kelly Roussi

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Executive Brief

Welcome to the inaugural Geroscience Focus Report, developed by the Insights Publications Team at Crystallise Ltd. This bulletin series aims to provide an accessible yet rigorous overview of key topics in geroscience that may influence human health and lifespan. Our target audience includes anyone concerned with longevity risk including executives and modellers in the insurance industry, but also those working in public health and policy. We aim to equip these readers with a mental framework for understanding geroscience concepts that could impact longevity risks, helping them to follow relevant discussions in professional literature and to communicate effectively with colleagues about the emerging field of gerotherapeutics — interventions designed to slow the biological ageing process.

Our typical readers are highly educated non-specialists with limited time. To meet their needs, we provide a concise digest of evidence and simplified cognitive models of key concepts drawn from both academic and 'grey' literature — including reports, white papers, and other authoritative sources. This content is designed to be consumed in minutes rather than hours. We consciously avoid an overly academic style, instead focusing on accessible summaries, while intending to provide further detail in subsequent articles, reports, and white papers that elaborate on our methods and processes.

Geroscience Focus will be issued quarterly for our subscribers, with each edition comprising three main sections:

- Two **Essentials articles,** covering important aspects of geroscience. In this issue we dedicate the first of these to an explanation of the 'hallmarks of ageing', which are a framework for understanding the mechanisms of ageing as they are presently understood. The hallmarks of ageing will be referred to frequently in future bulletins. The second provides a description of the modelling methodology we use in the Geroscience Spotlight article, using disease-specific ageing rates to translate findings in animal models into humans.
- A **Spotlight article** where we investigate a potential gerotherapeutic intervention in detail, exploring which mechanisms of ageing it may affect and which ageing-related diseases could be eased. We will explore the potential impact using our own model of ageing, and discuss the implications for insurance products exposed to longevity risk. Most of the evidence we have is in animal models and how or if these effects translate to humans is, at present, unknown. We make a basic assumption that there is a proportional effect in humans, adjusted for the impact on the hallmarks of ageing and the associated ageing-related diseases (ARDs). This results in a discounted reduction in ageing in humans compared to laboratory mice. We also provide an analysis using an ageing reduction rate (ARR) reduced by 50% on the assumption that the longer lifespan of humans results in a lower ARR than that seen in test organisms with a shorter lifespan. We then compare the change in life expectancy for a 65 year-old today and a 65 year-old in 25 years' time.

Dr Chris Martin
Managing Director, Crystallise Ltd

Geroscience Essentials – The Hallmarks of Ageing

Ageing as a target of intervention

Medical care typically involves identifying a disease state and matching it to an appropriate treatment. The premise is that the more specific a diagnosis can be made, the more specific and effective the treatment can be.

Preventative medicine aims to prevent a disease state from occurring in the first place by targeting underlying risk factors, often reducing the risk of many diseases across multiple organs. A huge risk factor for most causes of death is old age, and yet age is not usually considered modifiable in the way other risk factors such as high blood pressure, obesity, and smoking are when considering disease prevention. However, we all recognise that there is a significant difference in biological and chronological age, and gerotherapeutics aim to slow the rate of biological ageing. While lifestyle interventions like exercise and dietary restriction already offer promising results, emerging pharmaceutical candidates hold potential to further advance this goal.

One barrier to studying age as a risk factor is its multiplicity – it is not a single process that can be considered in isolation, but a slow, system-wide deterioration in function. In principle, there is no reason why the underlying processes of ageing cannot be studied and interventions developed.

Ageing-related diseases

Ageing-related diseases are conditions where the observed relationship between the process of ageing and the incidence of the disease is causal. Some conditions are age-related or age-associated without being ageing-related. For example, childhood infectious diseases and pregnancy-related deaths are age-related, but not *ageing*-related. There are arguments around whether some apparently ageing-related conditions are merely the accumulation of damage from environmental exposures, but the difference could be considered somewhat philosophical as it can be argued that the hallmarks of ageing result from these exposures anyway, with the possible exception of telomere shortening. For this exercise, we make an assumption that diseases where a Gompertz model of ageing has a good fit to the incidence rate, the disease is ageing related.

The Hallmarks of Ageing

The Hallmarks of Ageing framework attempts to define conceptually distinct processes that together cause the decline in physiological function and increased vulnerability to diseases that characterise ageing.[1] A hallmark is not a single biochemical pathway and it does not occur only in a single cell type, tissue or organ. Instead, they are general processes occurring at the molecular and cellular level throughout the body. To qualify as a hallmark they must:

- Have an ageing-associated manifestation
- Accelerate the rate of ageing when promoted
- Decelerate, stop, or reverse ageing when appropriately inhibited.

Although the hallmark processes are interconnected through biochemistry and cell signalling, considering them as distinct mechanisms can bring structure to our understanding of ageing. Although drugs tend to have very specific target molecules, by linking a gerotherapeutic to particular hallmarks, and those hallmarks to sets of ageing-related diseases, we may be able use the sparse causal data to produce better estimates of a future mortality profile. We can also identify which hallmarks are likely to be most important from a mortality perspective.

Twelve distinct hallmarks have been described in the literature. Some of the hallmarks are '***Primary***', in that they are the fundamental drivers of the process of ageing. '***Antagonistic***' hallmarks are the result of responses to damage that might serve some beneficial purpose in the short-term, but become detrimental over time. '***Integrative***' hallmarks result from the combined effects of the 'primary' and 'antagonistic' hallmarks leading to functional decline. These hallmarks are considered points-of-entry for gerotherapeutics, but the attenuation of one will likely affect other hallmarks in the network.

Figure 1: The twelve Hallmarks of Ageing [1]

Primary

Telomere Shortening	Telomeres are DNA caps on the ends of chromosomes like the plastic tips at the ends of shoelaces. With each cell division, these 'tips' get shorter, eventually exposing the chromosomes to damage and increasing mutation rates, leading to cell ageing and death.
Epigenetic Alterations	Epigenetics refers to the processes that control gene activity, without changing the genetic code. It is often influenced by environmental factors, turning genes on or off in order to protect the body or enable it to adapt.
Loss of Proteostasis	Proteins are the building blocks of the body, essential for structure and function. If their production is faulty, the body deteriorates. Once a gene's instructions are used to create a protein chain, this chain must fold into the correct shape to function properly. Defects in protein folding can result in non-functional or harmful proteins that accumulate, such as amyloid plaques in Alzheimer's disease.

Disabled Macro-autophagy

Macro-autophagy is the body's recycling system. When disabled, waste and damaged components accumulate inside cells, leading to a build-up of dysfunctional cells and an acceleration of ageing.

Genomic Instability

Genomic instability refers to the accumulation of damage to the DNA structure and sequence beyond the age-diminishing capacities of repair mechanisms. This damage is also transmitted to the new cells when they divide. Cell growth, repair, maintenance, division, and behaviour rely on signalling between the DNA, the rest of the cell, and its environment. Particular genes are often found to have DNA mutations in cancer cells.

Antagonistic

Mitochondrial Dysfunction

Mitochondria, located inside the cells, are responsible for producing the energy needed for various cellular functions. Dysfunctional mitochondria are inefficient users of energy which generate toxic by-products such as 'reactive oxidative species' (ROS), which can damage cellular components. Mitochondrial dysfunction is like having faulty, leaky batteries, leading to less energy and more cell damage over time.

Cellular Senescence

Cellular senescence is a process where cells stop dividing, show changes in morphology, and change the molecules they secrete. It is an active process, with adaptive roles in wound healing and embryo development. However, during ageing the clearance of these cells becomes impaired and they accumulate, disrupting tissue function and repair.

Deregulated Nutrient-sensing

Deregulated nutrient sensing occurs when the body's ability to properly detect and respond to nutrient signals such as amino acids and glucose is impaired. This can lead to excessive cell division and growth, and the inhibition of the recycling of cellular components, and inflammation.

Integrative

Chronic Inflammation

Chronic inflammation is the ongoing presence of inappropriate or unprovoked inflammation. Inflammation is an important part of the immune process and of tissue repair mechanisms. However, continuous inappropriate activation of these processes can result in dysfunction and damage to tissues. Senescent cells secrete molecules that contribute to chronic inflammation.

Altered intercellular Communication

Altered intercellular communication occurs when cells in the body struggle to send and receive signals correctly, disrupting their ability to work together. This miscommunication can lead to problems like chronic inflammation, impaired immune responses, and disrupted tissue repair.

Dysbiosis

Dysbiosis occurs when the balance of microbes in your body, especially in the gut, gets disrupted. This imbalance can lead to digestive problems, inflammation, and a weakened immune system. Just like a garden overrun with weeds, an overgrowth of harmful bacteria can crowd out the beneficial ones, disturbing the overall health of the body. This imbalance can contribute to a range of health issues and accelerate ageing.

Stem Cell Exhaustion

Stem cells are the body's repair system, used to regenerate and replace damaged tissues. Stem cell exhaustion occurs when the supply of these vital cells becomes depleted. As we age, stem cells lose their ability to renew themselves and produce new, healthy cells. This decline makes it harder for the body to heal injuries and maintain healthy tissues, leading to increased wear and tear and contributing to the ageing process and age-related diseases.

Geroscience Essentials – A Novel Approach to Modelling Gerotherapeutics

Background

Gerotherapeutics hold the promise of significantly enhancing quality of life and extending life expectancy by targeting ageing-related diseases: slowing their progress and increasing 'health span'. Unlike treatments targeting specific disease outcomes, modelling the impact of gerotherapeutics presents a complex challenge as they target the ageing process itself. There are huge uncertainties in how the findings of prolonged life expectancy in animals exposed to these agents would translate into humans. Whilst this prevents meaningful forecasting of outcomes, we can build speculative 'What-if' scenario models based on an assumption that these effects translate proportionally into humans. This can give an idea of the potential effects on longevity risk in insurance and pension portfolios.

Crystallise, in collaboration with a multi-disciplinary committee with expertise in actuarial science, geroscience, and medicine, has developed a 'gero-modulation' modelling approach. The approach is based on the following guiding principles:

1. **MULTIDISCIPLINARY**
   Capture the multi-disciplinary expertise available
2. **PRACTICAL**
   Easy and practical to use
3. **COMPREHENSIVE**
   Capturing effect size translation, slowdown in disease progression, combinations of treatments, timing of intervention take-up, access to treatments, and patient compliance
4. **POPULATION-BASED**
   Utilising population cause-of-death data to reflect the potential impact of therapeutics on life expectancy.

The primary objective of the Geroscience Focus report is to gather evidence on and model a specific gerotherapeutic each quarter. Over time, this will provide our subscribers with a comprehensive database of gerotherapeutics and their potential impacts. By comparing these to our initial distribution, we can evaluate their relative risks from a longevity perspective, and potentially improve upon our initial approximate distribution.

Modelling Framework

Based on these principles, Crystallise has developed a model framework with four key components aimed at determining a future biological age mortality profile. This decomposition allows for a better understanding of each real-world challenge facing gerotherapeutics. A key feature of this modelling is that it is the passage of time that is rescaled and not the base mortality rates as in standard cause of death modelling (Figure 2).

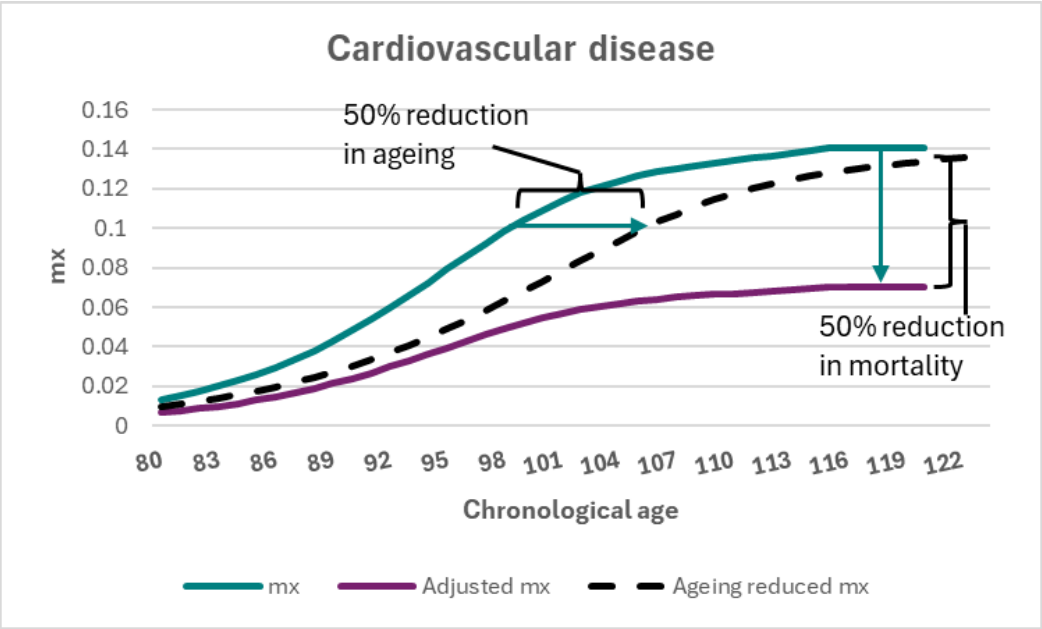


Figure 2. Figure showing how typical cause of death modelling scales mortality on the y-axis compared to an ageing model which scales the passage of time along the x-axis. Illustrated using cardiovascular disease and a 50% scaling factor for both mortality and ageing after adjustments for real-world factors.

The four components of the gero-modulation model is outline in Figure 3 below.

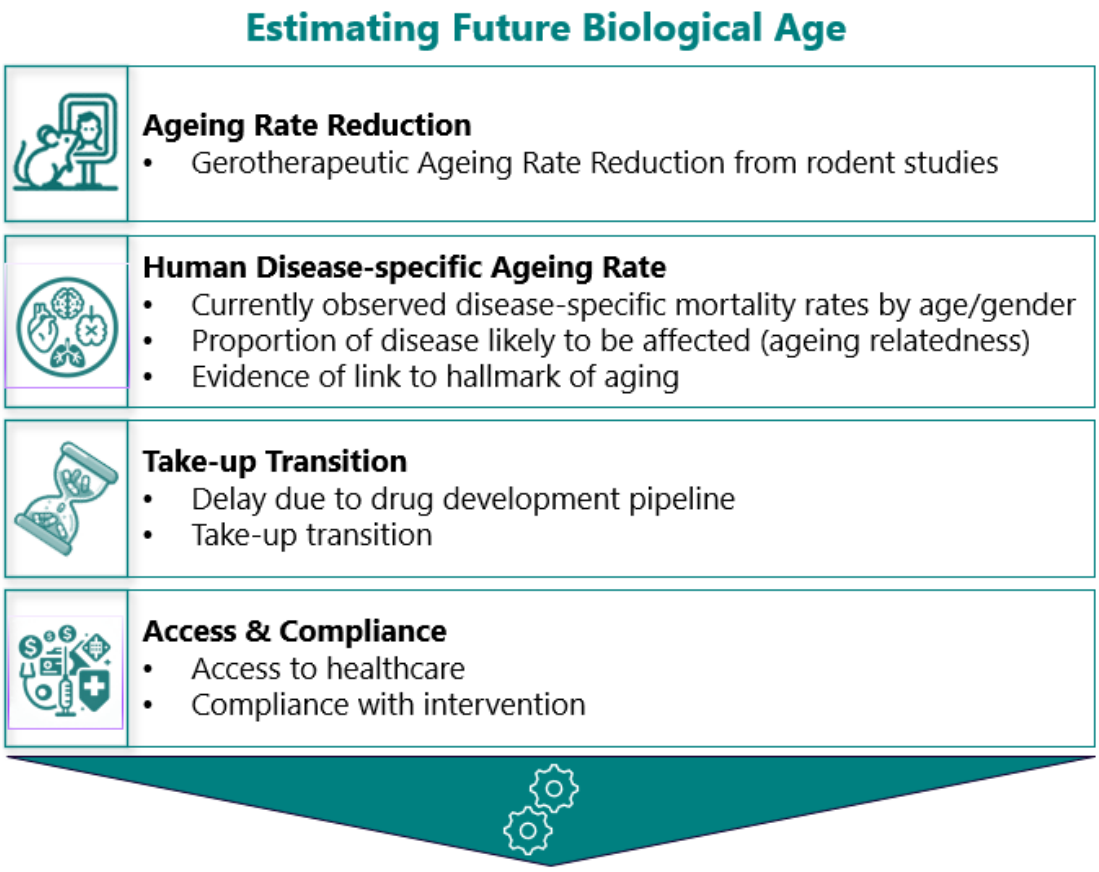


Figure 3: Approach to Gero-modulation modelling

Ageing rate reduction

- With human data lacking, animal studies (mainly in mice) are used to estimate gerotherapeutic effect sizes. ***This makes the assumption that similarity in the physiology and genetics between mice and humans will result in similar outcomes, which is far from certain***.
- Effect sizes are usually reported for animal studies in terms of changes to survival rates and life expectancy.
    - These are converted to changes in the rate of ageing through fitting a modified double Gompertz model.
- Within the model, changes in the rate of ageing are represented by separating chronological and biological age. This makes the assumption that ageing processes can be slowed, but not stopped or reversed.
    - An intervention that slows the rate of ageing allows a chronologically older individual to experience the lower mortality rate of a biologically younger one. From these updated mortality rates the new life expectancy can be calculated.

Human disease-specific ageing rate reduction

- Humans suffer mortality from a much larger range of causes than laboratory mice, including external causes such as traffic accidents. Laboratory mice almost exclusively die of cancer, which is a highly ageing-related cause of death.
    - The model tracks biological age for nineteen cause-of-death categories separately in humans. For example, the biological age for cancer mortality can be different from that for cardiovascular mortality.
- A disease that doesn't become more common with age is not ageing-related and so would not be expected to respond to ageing interventions. For each cause-of-death category, an estimate is made of how much of the disease burden is caused by ageing. This is based on the goodness-of-fit of the incidence by age to a Gompertz model for individual causes of death within the category.[2]
    - This ageing-relatedness value represents the maximum theoretical impact a gerotherapeutic can have on the rate of ageing for that cause-of-death category in humans.
- The association between different hallmarks of ageing and different ageing-related diseases has been estimated by mining the medical literature, analysing genetic databases and cross-referencing the results with real-world data in clinical records databases.[3,4]
    - For a particular intervention in humans, the modelled changes to the rate of ageing are only applied to cause-of-death categories that have been linked to the same hallmarks as that intervention. This implies an assumption that these associations are all-or-nothing, which is unrealistic, but necessary given the lack of data.

Mortality rate

The model is illustrative rather than predictive, so we can show how changes in longevity might unfold, given a certain set of assumptions. We need to project mortality rates into extreme old age, so we aggregated death counts by ICD10 chapter up to the age of 104 years between 2010 and 2019 so that there is greater stability in the data and fitted p-splines. Current opinion favours there being no plateau in mortality rates in the extreme elderly,[5] so we projected the mortality rate p-splines out to the age of 115 before applying a plateau.

Take-up transition

- The modelling is based on the scenario that a sufficiently effective and safe gerotherapeutic will eventually become licensed for use, which is highly uncertain.
- Once the biological effect of the intervention has been estimated, projection forward in time begins by estimating the time taken for uptake by the population.
    - This considers the current clinical trial pipeline, the likely timeline for regulatory approval and historical patterns of expansion of use of major medical innovations historically.

Access and compliance

- Finally, barriers to uptake and compliance are considered at the population level, which reduces the projected impact of the intervention.

Parameterisation Approach

Ageing Rate Reduction

Rodents, particularly mice, are frequently used in ageing research due to their genetic similarities to humans and their relatively short lifespans. Mice are also useful as they generally die from cancer, an ageing-related disease. In the past, the impact of gerotherapeutics on the lifespan of mice has been used to determine an estimate for their potential impact on humans.

Instead, our approach determines the effect on the ageing rate of mice (Ageing Rate Reduction or ARR) from survival data by fitting a double Gompertz. Figure 4 is a typical example of fitting to mouse model survival data.[6]

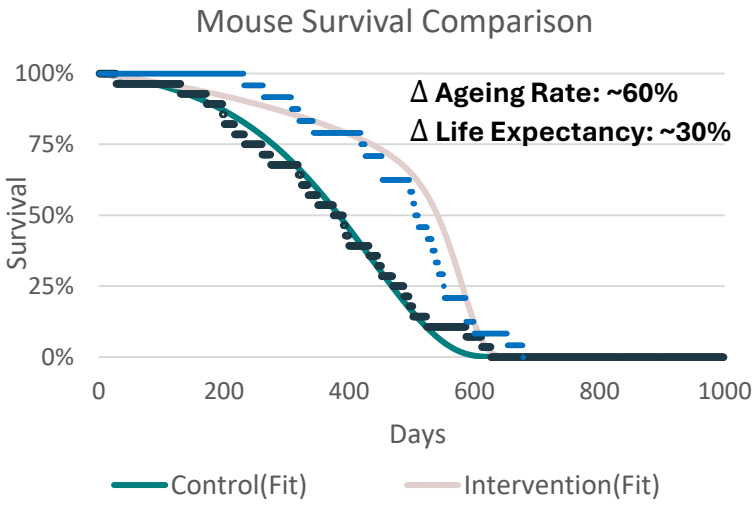


Figure 4: Exemplar fit of double Gompertz to mouse survival data following senolytic treatment. [6]

Human Disease-specific Ageing Rate

Biological ageing can be defined as "…an intrinsic and inevitable degradation of biological function that accumulates over time at every level of biological organisation from molecules to populations".[7] To model the impact of gerotherapeutics, we apply an Ageing Rate Reduction observed in laboratory studies in mice to human populations.

For example, a 50% Ageing Rate Reduction for a 50-year-old would result in an all-cause mortality profile broadly similar to that of a 60-year-old in 20 years even though they are aged 70 chronologically, reflecting a slower onset of ageing-related diseases, and a life expectancy increase of ~50% (Figure 5).

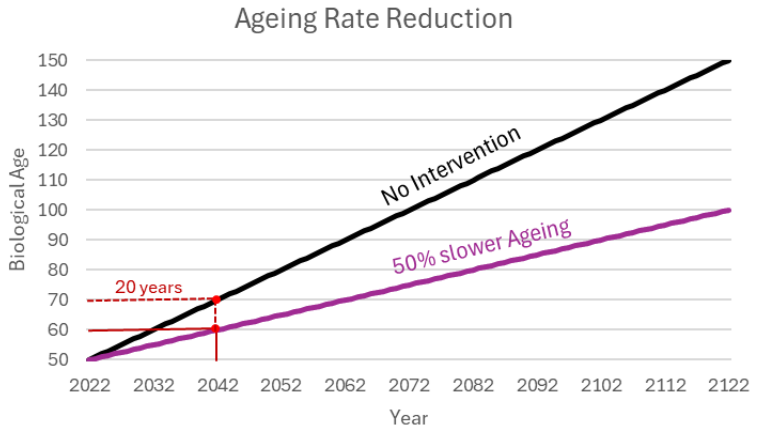


Figure 5: Illustration of 50% ageing Rate Reduction applied to chronological age

We use general population disease-specific mortality data combined with disease-specific Ageing Rate Reductions to estimate future mortality profiles. The disease-specific Ageing Rate Reduction is estimated based on:

- The proportional contribution of ageing to the risk of death by cause from the analysis by Kuan *et al* 2021 (e.g. ~86% for cardiovascular, but 0% for external causes, such as road traffic accidents).[2]
- The hallmarks that are attenuated by the gerotherapeutic, and the evidence linking that hallmark to a disease category (no evidence = 0, sufficient evidence = 1) in the form of textual associations in the medical literature and supported by ARD-ageing hallmark associations in a genetic database.[3] For example, targeting genomic instability would primarily impact cancers and blood disorder, whereas targeting deregulated nutrient sensing would significantly impact cardiovascular, endocrine, musculoskeletal and neurological disease, but not cancers.

For a 50-year-old, a gerotherapeutic targeting all hallmarks of ageing with 50% slowdown in the onset of hallmark-linked ageing-related diseases would result in a ~30% increase in life expectancy. Targeting a subset of hallmarks would result in a lower impact in our modelling. This approach allows us to reflect the underlying human morbidity and more accurately capture the effects on longevity of delaying disease incidence and increasing 'health-span'.

Take-up Transition

The take-up transition from clinical trials to widespread adoption is critical for the impact of gerotherapeutics on public health. Following regulatory approval, uptake involves a gradual process influenced by healthcare infrastructure, regulation, awareness, and socioeconomic factors. On examining historical medical innovations such as statins and aspirin for cardiovascular diseases, it can be seen that adoption rates are initially slow, but accelerate as data on efficacy and safety grow. This transition spans decades. Our model accounts for this by delaying and transitioning the Ageing Rate Reduction. For example, delaying the availability of a gerotherapeutic by just 10 years would result in the average 50-year-old today losing approximately 1/4 of potential added years.

Access and Compliance

Access to and compliance with gerotherapeutics are pivotal for their real-world effectiveness. Even promising treatments can fall short if not widely accessible or if patients do not adhere to regimens. Access issues stem from healthcare infrastructure, socioeconomic disparities, and geographic barriers. Compliance depends on patient awareness, perceived benefits, and overall healthcare engagement. Historically, typical compliance with treatments is around 50%, but this varies. Our model adjusts the expected efficacy (Ageing Rate Reduction) to account for expected changes in access and compliance over time, ensuring projections are grounded in practical realities.

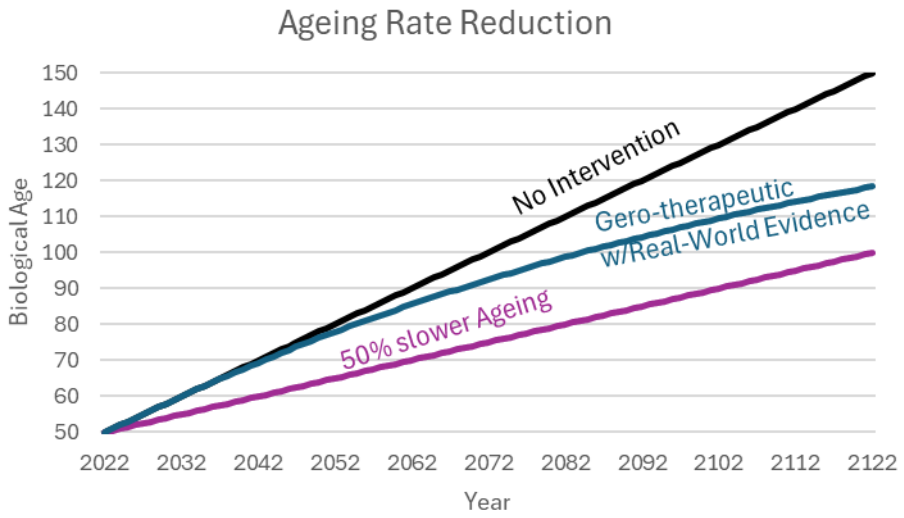


Figure 6: Illustration of real-world factors reducing effectiveness of Ageing Rate Reduction

Limitations

- Our modelling explores a particular scenario where the effect observed in laboratory mice is translated to humans. There are huge uncertainties in the effect that gerotherapeutics would have on humans. For example, dietary restriction appears to consistently increase lifespan in all the animal models tried so far, but the effect size appears to diminish with increasing lifespan of the organism. It is possible that this is also true of gerotherapeutics.
- Our understanding of the processes of ageing is at an early stage, and the classification of the hallmarks of ageing continues to evolve. Whilst they are regarded as distinct entities, they are all connected and interact.
- We have selected the hallmarks of ageing – ageing related disease pairings by applying a threshold to the measures of association, which is essentially arbitrary.
- We have used measures of the association of hallmarks of ageing and ageing-related diseases derived from text mining and analysis of genetic databases. This is supported by an analysis of comorbidities in clinical databases but should still be regarded as uncertain.
- There may be reasons why widespread use of gerotherapeutics may not be suitable, such as toxic effects unrelated to ageing and concern about unknown long-term effects. It is also possible that they are not found sufficiently safe or effective for use at all. We do not capture these uncertainties in our modelling.
- We use one measure of the rate of ageing in the modelling. However, ageing is driven by several independent processes that may well have different rates of ageing and respond differently to any particular gerotherapeutic.

Model Application

The model generates cause-of-death mortality tables for future ages and years, enabling the estimation of life expectancy for both current and future populations. For instance, annuity providers can assess the impact on their current portfolios for reserving purposes or to devise pricing strategies for future pensioners. Additionally, policymakers can use the results to understand the importance and impact of expediting the drug regulatory process.

Geroscience Spotlight - Rapamycin (mTOR inhibitors)

This article aims to give a basic understanding of what mTOR is and what it does, what mTOR inhibitors do and how inhibition may impact ageing by influencing seven of the twelve hallmarks of ageing, as described in the accompanying article, thereby potentially reducing the rate of ageing. We model the potential impact of mTOR inhibitors on ageing in humans by extrapolating data from trials of mTOR inhibitors in mice, using evidence on the way mTOR inhibitors impact the hallmarks of ageing and how those hallmarks of ageing affect the different profiles of ageing-related diseases in humans and mice. We estimate the impact on life expectancy in a 65-year-old today, and in a 65-year-old in 25 years' time under a default assumption that treatment would not start until the age of 50 years when it is available.

The biology of mTOR

mTOR activation stimulates growth and cell proliferation in response to abundant nutrients, oxygen and energy. It is a naturally occurring protein in our bodies that ***plays a critical role in growth and development*** and is an important pathway in the regulation of ageing and the development of ageing-related diseases. When food is plentiful, mTOR senses this abundance and signals cells to grow and multiply faster, producing more protein, fats and cholesterol. In young people who are growing, or in older people who exercise, this is necessary for growth and maintenance of muscle mass.

However, ***as people age, mTOR can become chronically over-activated***, and can result in an over-abundance of inefficient and dysfunctional cells which contribute to the effects of ageing.[8,9] Inhibition of mTOR reduces the size and quantity of cells, but promotes the function of quality control mechanisms, improving their efficiency.[10] As people get older, this reduces the rate at which the inefficient and dysfunctional cells accumulate, and reduces the rate of ageing.

mTOR is not a 'bad thing', it is clearly a vital component of the physiology of nearly all animals and some plants and fungi. However, chronic over-activation has its disadvantages, particularly in those who have stopped growing. Similarly, ***mTOR inhibitors are not necessarily always a 'good thing'***. If that were the case, mTOR would not have evolved as a process at all. These processes are complex and dynamic with the optimal balance between activation and inhibition shifting according to context.

It is important to think of mTOR activation and inhibition as being a continuous variable. At an individual molecular level, it is binary, but the proportion activated across the many trillions of molecules behaves in an analogue fashion. Think of it as a volume control rather than an on/off switch. The following illustrates the impact of mTOR activation and inhibition:

- When mTOR is activated, it causes cells to grow quickly and multiply, allowing growth, development and the building of a robust organism, but it may lead to a shorter lifespan.
- When mTOR is inhibited, cells focus on recycling and efficiency, which can lead to a longer and healthier life, but possibly at the expense of loss of vigour.

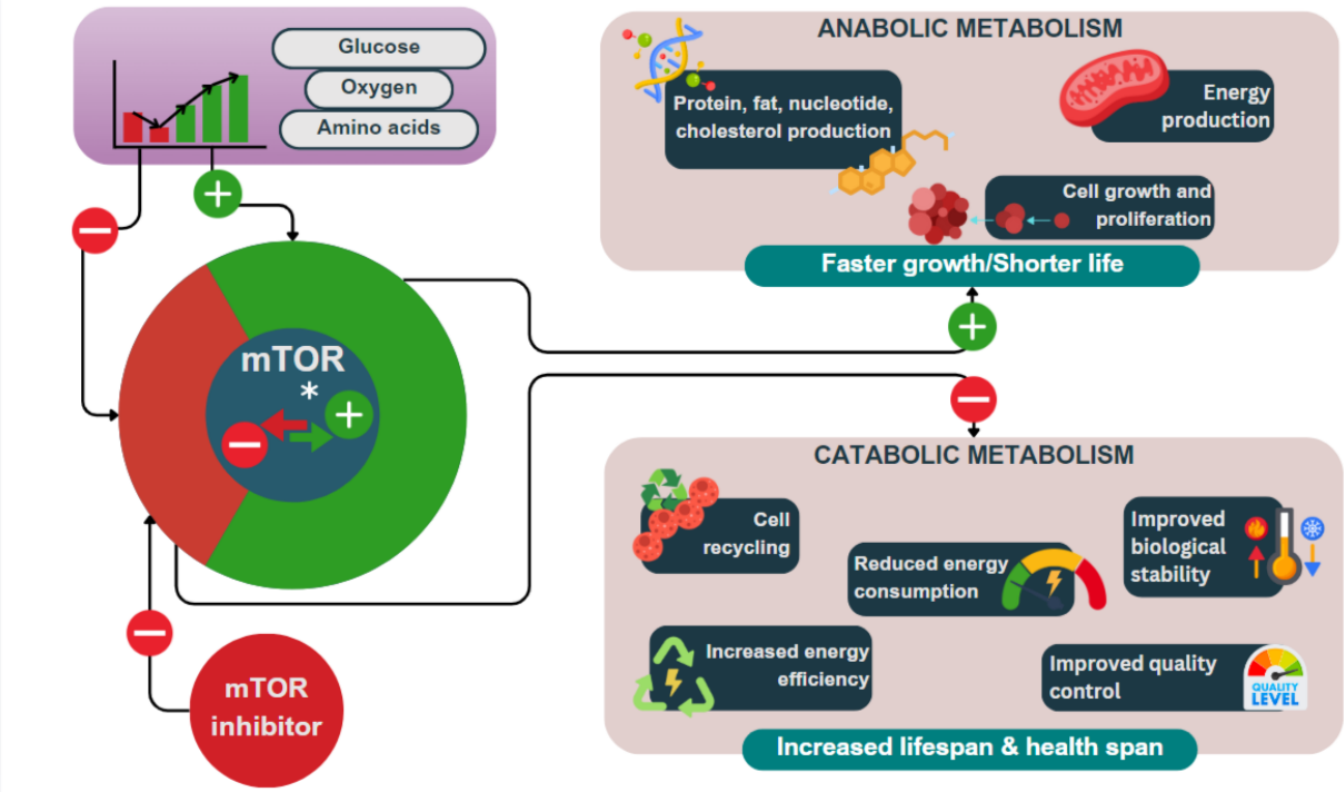


Figure 7. Biological process for mTOR inhibition with nutrient influencers and mTOR inhibitors role.

Lifestyle and behavioural factors can influence mTOR activation and inhibition.

- **Diet -** Low glucose levels inhibit mTOR, whereas high protein diets activate it. Hormones including insulin, and Insulin-like Growth Factor (IGF-1) secreted in response to dietary intake of sugars can also activate mTOR.
- **Exercise -** The relationship with exercise is complicated. Resistance training increases mTOR activity. During and immediately after aerobic exercise, mTOR activity is reduced, but within a few hours, mTOR activity is increased. In contrast, resistance training can activate mTOR from the outset. However, exercise also stimulates recycling systems in cells (autophagy) via other mechanisms which results in 'balanced activation' of mTOR where mTOR activity is regulated in such a way that it supports protein synthesis, muscle growth and cell metabolism without the negative effects of chronic over-activation. Cells become focused on recycling and efficiency, which can lead to a longer and healthier life despite the activation of mTOR. Decreased oxygen in tissues, such as can be experienced during exercise, can inhibit mTOR.

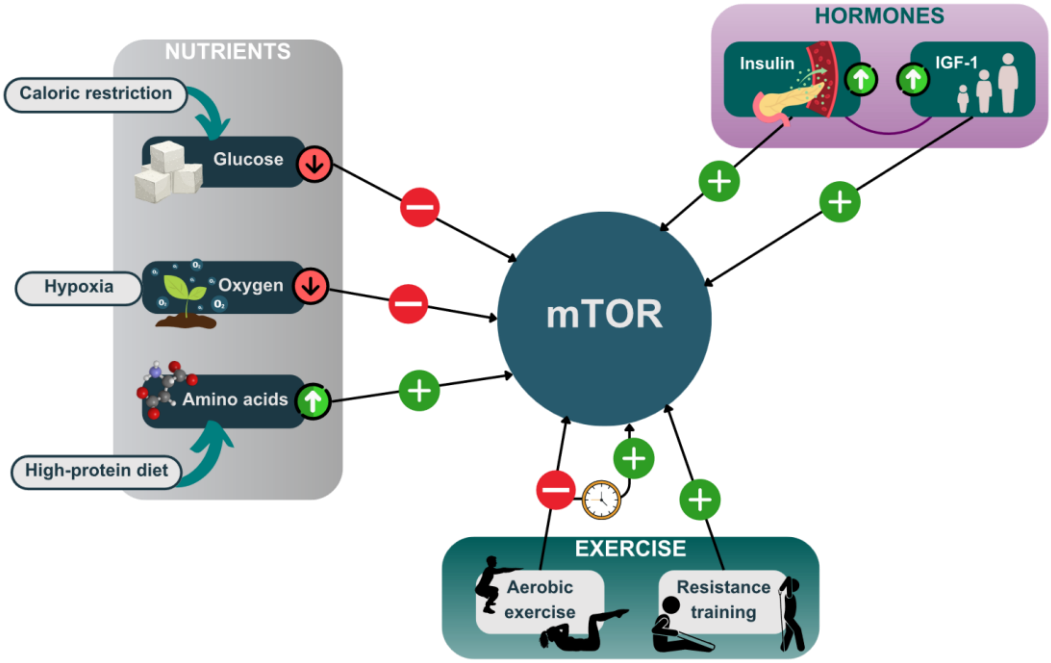


Figure 8. The influences on mTOR including nutrients, hormones, and exercise, and their impact on the mTOR pathway

Rapamycin, also known as sirolimus, was first discovered in the soil from Easter Island (Rapa Nui), hence its name.[10] It was first isolated in 1972, and initially studied for its antifungal properties, it was later found to have immunosuppressant and anti-cancer effects. Its first licensed use, under the alternative name of 'sirolimus', was in 1999 as a treatment to prevent the rejection of transplanted organs. In 2008-2009 it was found to extend the lifespan of laboratory mice.[11] It has since been found to increase lifespans in a range of organisms from nematode worms to rodents.[12]

Rapamycin was the first mTOR (or *'mechanistic target of rapamycin'*) inhibitor to be identified, and this, along with other so-called first generation mTOR inhibitors that bind to the same site as rapamycin, are called rapalogs. The other first generation mTOR inhibitors include temsirolimus, everolimus, ridaforolimus, umirolimus, torkinib, and zotarolimus.[13]

Second-generation mTOR inhibitors are now in development as anti-cancer drugs. The mode of action is to interfere with the regulation of the energy supply to the mTOR protein, and so prevent its functioning. These include sapasinertib, vistusertib, and samotolisib, none of which has yet been licensed for use.[13]

A third generation of mTOR inhibitors, currently in early stages of development, is being explored as potential anti-cancer drugs. These inhibitors also target another family of signalling proteins known as PI3K, which is similarly associated with cell growth and proliferation. An example of such a drug is omipalisib.[13]

Further information is given in the "Drug Development & Take-up" section.

Targeting the Hallmarks of Ageing

By understanding which hallmarks of ageing are targeted by a gerotherapeutic, we can better predict the diseases that are likely to be delayed. There is sufficient evidence to suggest rapamycin and other mTOR inhibitors attenuate the hallmarks of ageing broadly (7 of the 12).

Figure 9. mTOR inhibitors target 7 out of 12 hallmarks of ageing

The table below describes how seven of the hallmarks of ageing are targeted by mTOR inhibitors.

Deregulated nutrient sensing
mTOR is the principle signalling molecule for nutrient sensing. Characteristically, mTOR becomes over-activated with age, so mTOR inhibitors would help mitigate this over-activation.[9]

Cellular senescence
mTOR inhibition slows down the rate of development of senescent cells, and could even reverse some senescence present in cells.[9]

Mitochondrial dysfunction
mTOR inhibitors increase cell recycling, including mitochondrial components, resulting in a reduced proportion of dysfunctional mitochondria.[9]

Disabled macro-autophagy
mTOR down-regulates cell recycling (autophagy) as it promotes the expansion and proliferation of cells. This decreases the rate at which dysfunctional cells and cell components are removed and contributes to ageing.[9] These effects might be mitigated using mTOR inhibitors.[9]

Loss of proteostasis

mTOR promotes protein production and so increases the burden on the mechanisms needed for maintaining protein integrity in the cell thus increasing the accumulation of damaged proteins. Maintenance of protein integrity requires energy. mTOR inhibition improves efficiency of the mitochondria in cells, which are responsible for energy production.[9]

Stem cell exhaustion

mTOR inhibition appears to increase stem cell numbers and function, in particular in the blood and intestines. This is partly through the process of de-differentiation, where specialised cells revert to a more stem cell-like state.[9]

Chronic inflammation

mTOR affects the regulation of certain messaging chemicals that control the inflammatory response. mTOR activation also enhances cell proliferation – a process essential to the immune response, which involves the increased production of immune cells.[9] These effects might be mitigated using mTOR inhibitors.

Ageing-related diseases

We would expect the hallmarks of ageing being targeted above to have an impact across most of the key ageing-related diseases.

Cancers

mTOR activation promotes cell growth and proliferation and reduces the rate at which dysfunctional cells are destroyed. This is a necessary part of the malignant process. Inhibition of mTOR can reduce the rate at which cancer cells grow and proliferate, and accelerates the removal of dysfunctional cells.[13]

Cardiovascular disease

mTOR inhibitors can improve the health and functioning of the cells lining arteries. They have been found to reduce the formation of 'endothelial plaques', the thickening of the inside of arteries that is a critical step in the development of atherosclerosis.[14] Using coronary artery stents that leach rapamycin into the surrounding tissues reduces the risk of restenosis.[15]

Respiratory disease

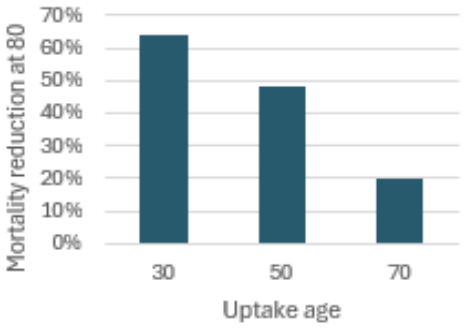
The evidence for a positive effect of mTOR inhibitors on respiratory disease is sparse. However, there are theoretical reasons to believe that there are potential benefits. Chronic respiratory disease often includes chronic inflammation and fibrosis as part of the pathological process. mTOR inhibition reduces inflammation and may reduce the process of fibrosis, which is reliant on cellular proliferation.[15]

Neurodegenerative disease

Enhancing cell recycling, downregulating protein production and improvement in quality control of proteins by inhibition of mTOR may slow down or prevent the accumulation of harmful misfolded proteins involved in neurodegenerative diseases, such as Alzheimer's disease and Lewy body disease.[15] Genetic downregulation of mTOR, which has the same effect as mTOR inhibition, has been found to mitigate the process of dementia in mouse models.[16]

Ageing Rate and Reduction in Mortality

We analysed the results of 13 laboratory trials involving a total of over 8,000 mice, estimating the effect size of targeting mTOR inhibition.[12] Following a meta-analysis of the data fitted to our modified Gompertz model, we estimate a 39% (95% confidence interval 31% to 46%) reduction in the rate of ageing. There is a great deal of uncertainty on how the ageing rate reduction in mice might translate to humans. It has been suggested that the ageing reduction from interventions like dietary restriction may have an inverse relationship with the lifespan of the model species. This would suggest the ageing rate reduction in humans would be limited compared to smaller mammals like laboratory mice. To take account of this uncertainty, we perform two analyses, one with the full 39% ageing rate reduction seen in mice, and another one with half of that – 19.5% ageing rate reduction. We present the survival curves based on an evaluation year of 2024 (now) and 2049, in 25 years' time. For reference, the survival curves for effect sizes from 10% to 100% in steps of 10% are also presented.



Mortality Reduction at age 80	Age at uptake		
	30	50	70
	64%	48%	20%

Figure 10: bar chart of maximum plausible mortality reduction at age 80 given a 39% ageing rate reduction; Mortality Reduction for uptake of treatment at ages 30, 50, 70.

Using our gero-modulation cause-of-death mortality model, we are able to examine the effects of a change in ageing rate on human mortality. For more information on the modelling approach, see the "Geroscience Essentials – A Novel Approach to Modelling Gerotherapeutics" section.

Figure 10 illustrates that the younger a person begins taking gerotherapeutics that slow ageing processes, the greater the potential impact on future mortality rates. For older individuals, the impact is lower due to higher likelihood of irreversible comorbidities and less time to delay future disease progression.

Using our base ageing rate reduction value of 39%, a naïve prediction of starting mTOR inhibition from age 30 would be to anticipate the possibility of a 64% reduction in all-cause mortality rates at age 80, reflecting slower disease progression over the preceding 50 years.

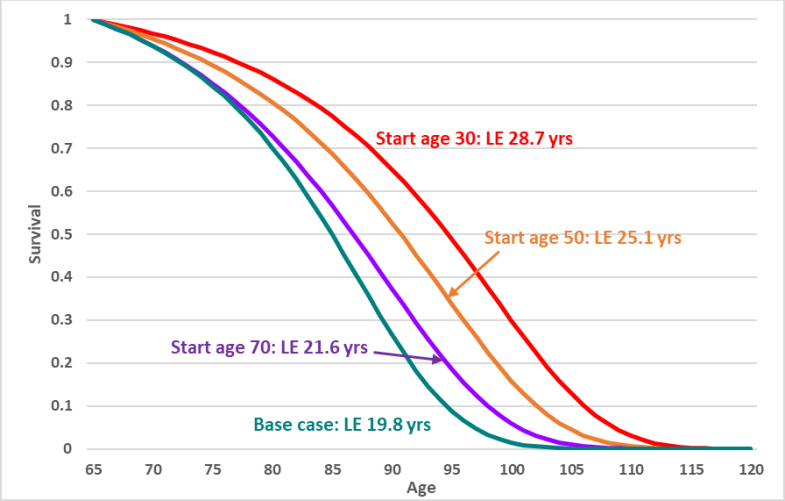


Figure 11. The impact of the start age on survival. These are survival curves for a 65 year-old with start ages for treatment of 30, 50 and 70 years, with the base case of no effect. There is no transition applied so there is the full effect starting immediately.

Figure 11 demonstrates the importance of the age of commencement of treatment, as the effect is cumulative over time. This scenario assumes that there is no adoption transition, that the full impact of treatment is felt immediately, and that treatment has been available for at least 35 years, so that our 65-year-old man will have been taking treatment from the age of 30, 50 or 70 years depending on the scenario.

However, at younger ages and over longer treatment spans, any negative impacts of mTOR inhibition on health are likely to be more material. A more reasonable expectation would be for treatment to start at older ages where clinical confidence of a net positive health impact will be higher. We apply a treatment commencement age of 50 years by default in our scenarios unless otherwise stated as ageing-related diseases (ARDs) tend to dominate mortality after this age.

There may be groups where specific gerotherapeutics would result in negative outcomes. In women at risk of pregnancy, it may not be wise to offer mTOR inhibitors as a gerotherapeutic regardless of age, as that may have negative effects on the pregnancy and development of the foetus.

The predicted difference in impact between males and females is otherwise immaterial (<1%), with females experiencing a slightly higher reduction due to a greater proportion of ageing-related mortality and fewer accident-related deaths. This difference is likely more significant among socioeconomic groups where external causes of death, such as drug abuse, self-harm, and other deaths of despair, are more common.

We will now add the possible real-world impact of delays in drug development and take-up of a gerotherapeutic targeting mTOR inhibition based on biomedical evidence and expert insights and reflect this in our gero-modulation modelling.

Drug Development & Take-up

Pipeline Analysis

To estimate the potential impact of delay from the drug development pipeline, we conducted an analysis of clinical trials up to May 8th, 2024. Our analysis used the AACT Database, extracting almost 500,000 clinical trials from the last 10 years.[17] We focused on trials investigating mTOR inhibitors relevant to ageing. The search identified 2,506 potential trials, from which we extracted more detailed information, including trial phases, indications, and interventions. We determined that 17 trials were directly targeting the ageing process, with an additional 254 targeting an ageing-related disease.

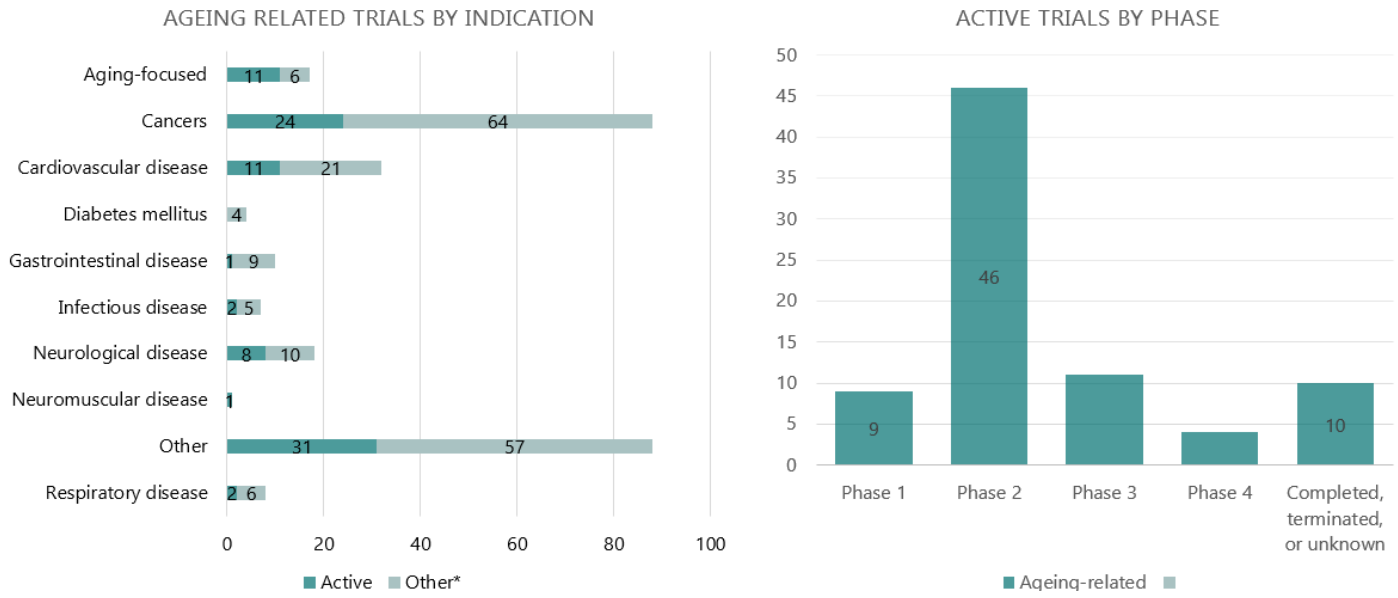


Figure 12: Results from analysis and categorisation of clinical trial pipeline data.

Potential drawbacks

All interventions have side-effects, of varying frequency and significance. At the doses used to slow down ageing, the most direct side-effects of mTOR treatment are minor, the most common of which is mouth ulcers, but skin rashes and stomach upsets are also reported.[15] However, despite these side effects being relatively trivial, they may be sufficient to deter people from continuing with the treatment, particularly if continuous administration is required.

mTOR activation is necessary for growth and development. Treated mice in some mTOR inhibitor studies were consistently smaller than untreated controls.[18] Injudicious use of mTOR inhibitors during periods of growth could stunt growth and result in loss of vigour. Exposure to mTOR inhibitors in pregnancy may affect the growth of the foetus, and women at risk of pregnancy should not take mTOR inhibitors if at all possible.[19]

There may be indirect consequences to the use of mTOR inhibitors that are significant. In well-nourished people undertaking exercise to build muscle bulk, it might be expected that there may be a reduction in the muscle mass achieved from resistance training in the short term as a consequence of blocking the activation of mTORC1 processes promoting cell growth, cell proliferation, and protein production. However, rodent studies suggest that this may not be the case, perhaps because reducing the rate of ageing would also be expected to reduce the loss of muscle mass usually seen with ageing (sarcopaenia).[20,21]

Barriers to implementation

There are barriers and factors that delay the implementation of any medical innovation. First, the effectiveness and safety of the intervention needs to be determined. The manufacturer can then seek a license for use, and if sufficiently cost-effective they can apply for approval from purchasers via health technology assessment (HTA). In the UK, this would be via National Institute for Health and Care Excellence (NICE) and in the US, various public and private organisation with protocols and principles similar to HTAs determine coverages. Finally, there needs to be infrastructure available to manufacture, distribute and deliver it at scale.

Table 1 shows a qualitative evaluation of the stage at which this technological innovation is in the journey from concept to use. Those rated '1' are at the beginning of the journey, and those rated '4' are at the end of that journey and are ready for immediate implementation.

Table 1. Summary of progress of mTOR inhibitors through implementation stages. 1) Initial=no progress or information at all; 2) Early=some progress or information but at an early stage; 3) Intermediate=substantial information and progress but not complete; 4) Advanced=Substantial and largely complete information and progress.

Area	Ratings			
	1) Initial	2) Early	3) Intermediate	4) Advanced
Effectiveness evaluation			✓	
Safety evaluation			✓	
Licensing and approvals			✓	
Manufacturing and scaling			✓	

Effectiveness evaluation - rating 3

There is evidence of effectiveness of mTOR inhibitors as a means of extending lifespan in a variety of animal models including rodents, but there are no human studies, and there may never be due to the timescales required to measure ageing reduction in humans.

Safety evaluation - rating 3

There is already a substantial body of data on side effects of drugs currently in use like everolimus. However, there may be more data to collect on larger scale or longer duration use.

Licensing and approval - rating 3

There are licensed mTOR inhibitors in use to treat cancer and as immunosuppressants, but there have been no license applications relating to reducing the rate of ageing as an indication. New applications under the indication of slowing down ageing may be more rapidly processed given the existing experience with these agents.

Manufacturing and scaling - rating 3

mTOR inhibitors are already being manufactured commercially for disease-specific licensed indications, but not for anti-ageing. The production is therefore scaled for the current indications, and would need to be increased significantly to service a broad anti-ageing indication.

Barriers to uptake

Once an intervention is available, it takes time for awareness and confidence in the benefits to accumulate in healthcare organisations, clinicians making treatment plans for patients, and the patients themselves. There are three major factors involved:

1. **Uncertainty and familiarisation**. For mTOR inhibitors, extensive experience is required to confirm the absence of unknown harms, such as rare but severe 'late effects.' Over time, accumulating evidence will refine the optimal use of mTOR inhibitors, reducing the uncertainty barrier and fostering confidence in their benefits. However, whilst there are examples of daily medications that impact pathology once thought of as age-related (e.g. hypertension medicines), these are not given to people considered healthy. Thus, in the short term, gerotherapeutic use may remain targeted, for example to improve vaccination effectiveness.[22]
2. **Compliance or concordance**. Adherence to prescribed mTOR inhibitor treatments varies among individuals. Evaluations of the interventions' worth can be both rational and irrational, and some people may struggle to remember to take their medication. Long-term preventive treatments like mTOR inhibitors are particularly vulnerable to non-compliance. The optimal timing for taking mTOR inhibitors as a treatment for ageing is uncertain. Using them before the age of 25 may be harmful due to ongoing growth and development. Starting treatment before the typical onset of degenerative diseases around the age of 50 seems reasonable, but determining when to stop is challenging. Eventually, ageing processes unaffected by mTOR inhibitors will diminish their benefits, which may vary by individual. Generally, treatment might need to be very prolonged, possibly for the rest of a person's life.
3. **Cost.** For healthcare systems, such as the NHS in the UK or insurers in the USA, having enough financial resources is essential to widely implement mTOR inhibitors. Extremely expensive treatments can cause financial instability, while very low-cost options might not be widely promoted due to limited profitability. Existing mTOR inhibitors, which have moderate production costs and could benefit many people, may be less likely to cause sudden financial strain. Rapamycin is off-patent and thus cheap, but newer-generation mTOR inhibitors would be far more expensive. Initially, access to these drugs might be given to those who would benefit the most such as those at higher risk of relevant ageing-related diseases, with broader availability expanding gradually over time.

Modelling Results

The evidence detailed in the previous sections was used to tune the four components of the gero-modulation model. This determined a set of scenarios specific to mTOR inhibitors:

- **Ageing Rate Reduction**: 39%. This is highly uncertain, so we do comparative analyses with ARRs of half that (19.5%) and each 10% increment in effect size from zero to 100%.
- **Disease-specific Ageing Rate**: There is sufficient evidence to attenuate seven hallmarks. Most ageing-related diseases are impacted. See "Geroscience Essentials – A Novel Approach to Modelling Gerotherapeutics".
- **Take-up**: Emergence is delayed six years from the start of phase 3 trials before the first drug indication is approved after taking into account the need for further research and development, and regulatory approval steps. This is an in-house view on the high, typical (medium) and low range of rate transitions into full use, reflecting uncertainty.
- **Access & Compliance**: An in-house view on a high, typical and low proportion of penetrance is used, reflecting uncertainty. These were based on a search of the literature for compliance and examination of trends in waiting and response times in the NHS.

Survival

We show how survival changes under our primary assumption of a 39% ARR translating to human ageing along with a halving of the ARR to reflect a reduced effect in humans who have a longer lifespan than mice, and also with each 10% increment of effect size from zero to 100% for context (Figure 13, Figure 14).

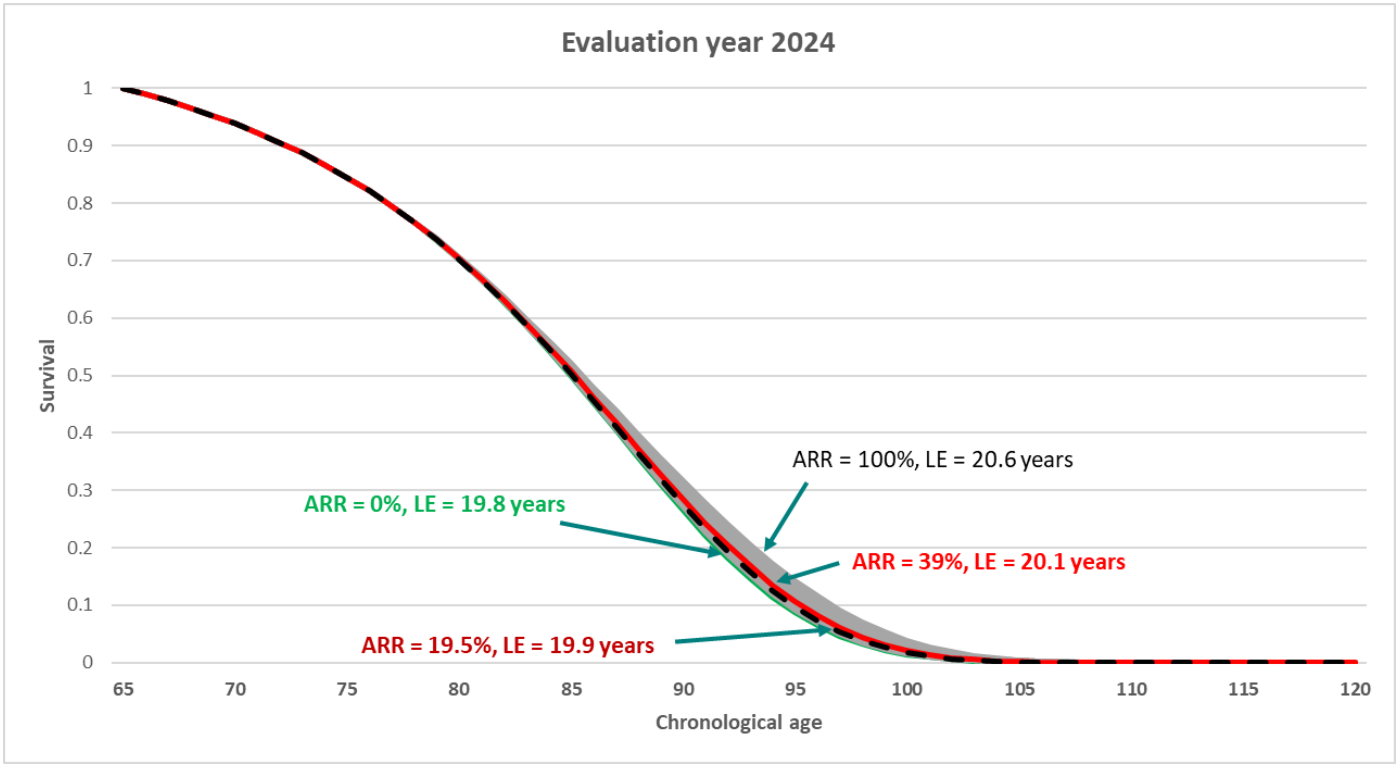


Figure 13. The survival curve for an untreated 65-year-old man who starts treatment as soon as it is available in green as evaluated in 2024, with the survival curves for 10%, 20%, ..., 100% ageing rate reduction in grey for comparison. The scenario of a 39% ageing rate reduction is in red, and the 19.5% ageing rate reduction is shown as the dashed black line.

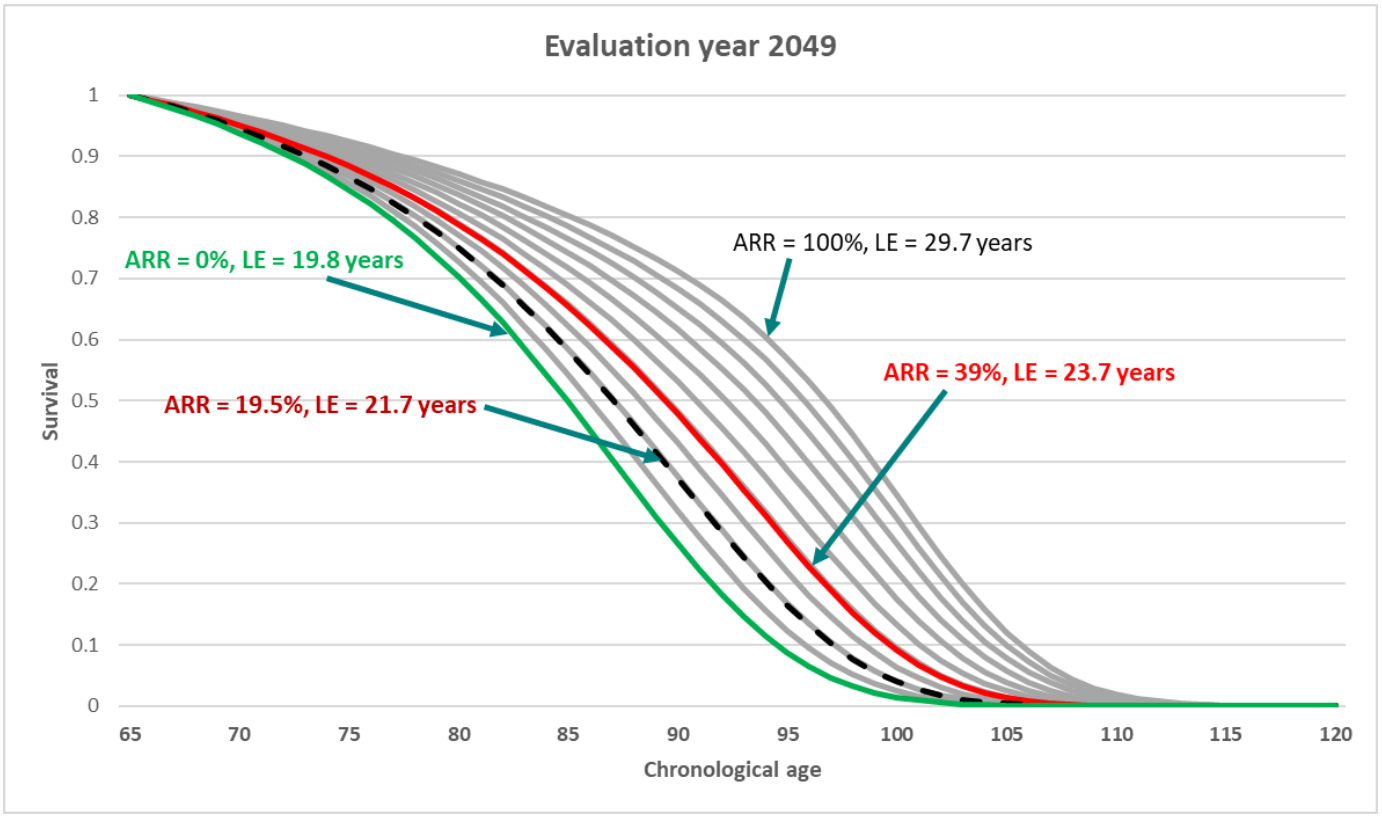


Figure 14. The survival curves for a 65-year-old man who starts treatment at 50-years-old in green as evaluated in 2049. The survival curves for ageing rate reductions in steps of 10% between 0% and 100% are in grey. The scenario of a 39% ageing rate reduction is in red, and the 19.5% ageing rate reduction is the dashed line. This is based on aggregated 2010-2019 mortality rates in England and Wales and makes an assumption that treatment starts at age 650. The 'typical' transition to uptake is used for all scenarios.

Timing of Mortality Improvements

In the longevity risk market, gerotherapeutics present a complex risk perspective. The potential to extend healthy lifespan and reduce ageing-related diseases presents a positive outcome for society. However, they also increase longevity risk for writers, placing increased uncertainty on reserves and the future pricing of longevity risk products.

Our model generates cause-of-death mortality tables for future ages and years, enabling the estimation of life expectancy for both current and future populations (see Geroscience Essentials – A Novel Approach to Modelling Gerotherapeutics for details). Using the real-world evidence on compliance and access rates, we have parameterised low, medium, and high impact scenarios for an mTOR inhibitor coming to market in the future. The impact of these scenarios on the timing of ageing rate reduction and on all-cause mortality improvements is shown below (Figure 15):

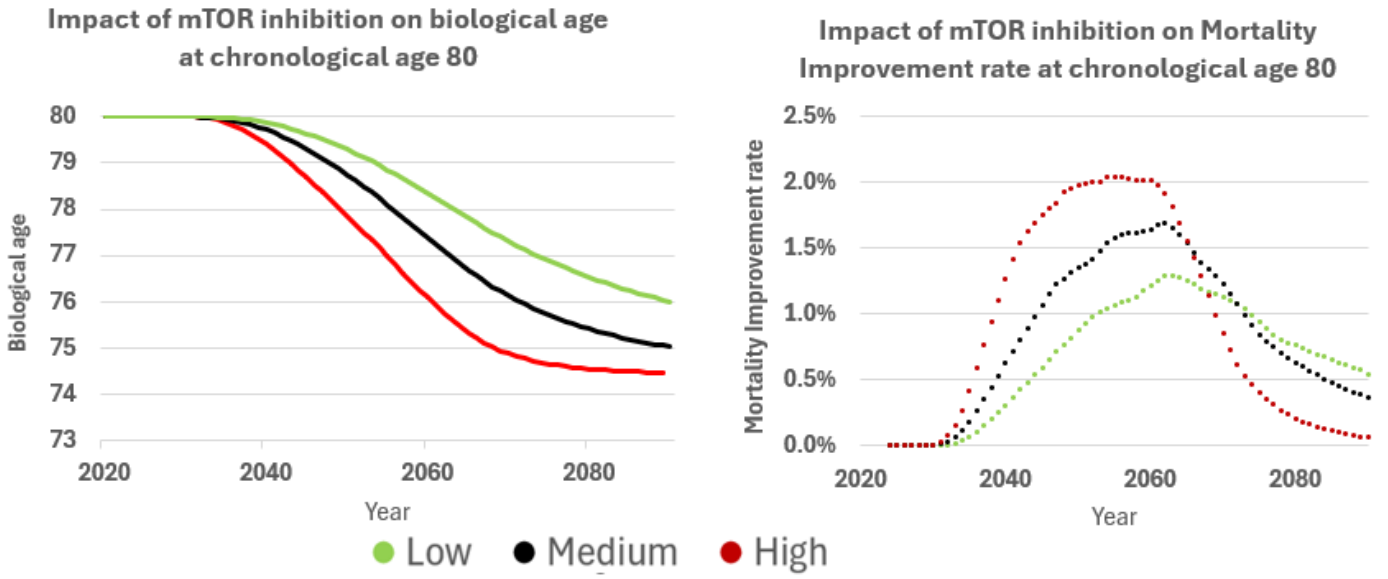


Figure 15. Ageing Rate Reduction & Mortality Improvements by impact scenario for a 39% reduction in the ageing rate for 80 year-old men who start treatment at age 50 years if it is available; left = reduction in biological age relative to chronological age in 2024; right = impact on mortality improvement rate over time (gender-neutral mortality rate, England 2022). The three scenarios represent the low, medium and high rates of transition for uptake. Compliance and access rates are constant across all three.

Initially, during the drug development phase, mortality improvements are minimal. Once the drug becomes available, improvements increase with societal acceptance and widespread use. Peak improvements occur at the peak rate of population uptake, followed by a decrease in gains as further improvements become harder to achieve.

Net ageing rate reduction

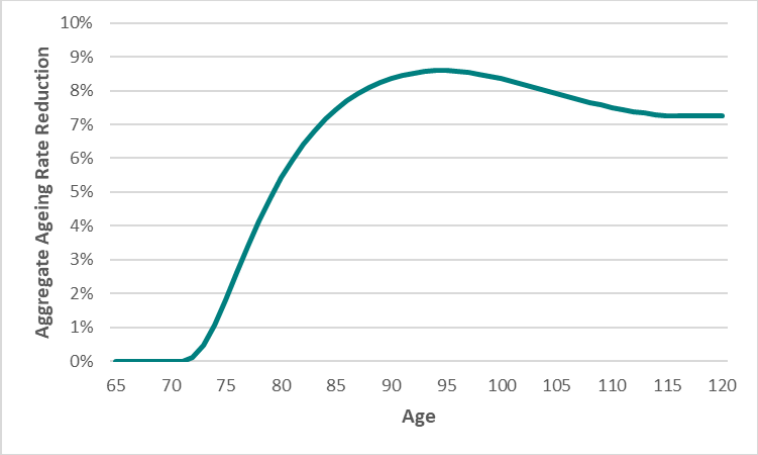


Figure 16. The net ageing rate reduction for a 65-year-old men who start treatment, when it becomes available, after translating a 39% ageing rate reduction in mice into humans for a 65-year-old man as evaluated in 2024.

Whilst we take the ageing rate reduction from the mouse studies, this is adjusted in humans by the ageing relatedness of the causes of death and the proportion of death at different ages relating to the different causes. We have estimated what the effective ageing rate reduction is after taking account of these mitigations and the delay and transition modelling. Figure 16 shows the effective ageing rate reduction for 65-year-old men in 2024 who starts treatment with mTOR inhibitors at that time under the assumption of a 39% ARR in mice. The ageing rate reduction in humans in this contexts peaks at just over 13%, or about a quarter of the rate observed in mice.

Life Expectancy

In order to demonstrate the impact on life expectancy, we consider two hypothetical populations:

- Age 65 now
- Age 65 in 25 years.

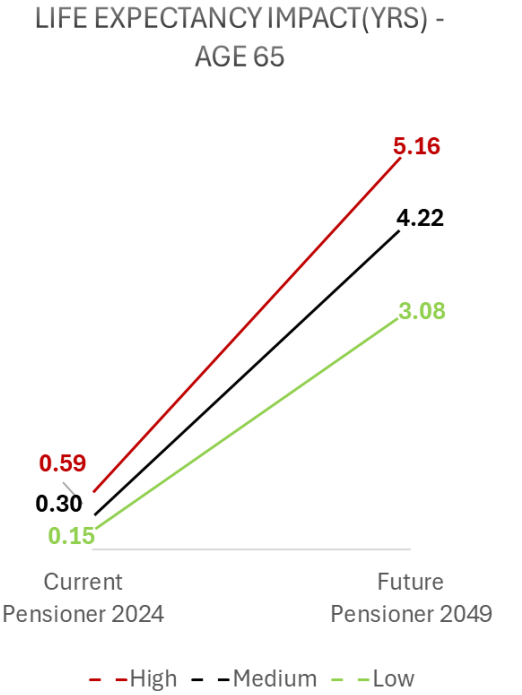


Figure 17: Life Expectancy Impact by impact scenario; gender neutral mortality, England 2022

This comparison allows us to assess the potential risk for insurers and pension schemes, both now and in the future, if they do not account for, or hold capital against, the advancements in gerotherapeutics.

In the high-impact scenario, an addition of 0.6 years to life expectancy represents approximately a 3% increase. The low-impact scenario shows negligible effects due to delays in the therapeutic pipeline. The gradient of these changes indicates the increasing risk over time. As gerotherapeutics approach availability, the impact on life expectancy becomes more pronounced, heightening the risk of mispricing and under-reserving by insurers.

Looking 25 years ahead, the high-impact scenario predicts an addition of 2.5 years, equating to a ~13% increase in life expectancy. This projected increase may surpass the current capital allowances held by some insurers. The male/female difference is immaterial, but this may vary in other sub-populations with significant mortality profile differences.

Going forward

mTOR inhibitors have the potential for significant impacts on life expectancy and should therefore be monitored closely by those managing longevity risk. Key indicators of risk include:

- Changes in the pipeline such as successful phase three trials
- New evidence of efficacy and safety from ongoing human trials
- Regulatory developments such as acceptance of ageing as an indication for treatment or accelerated pathways.

This is the first bulletin in a series that aims to shed light on the world of geroscience, focusing on real-world evidence and developing risk tools for longevity risk takers and policymakers to better navigate the longevity risk landscape.

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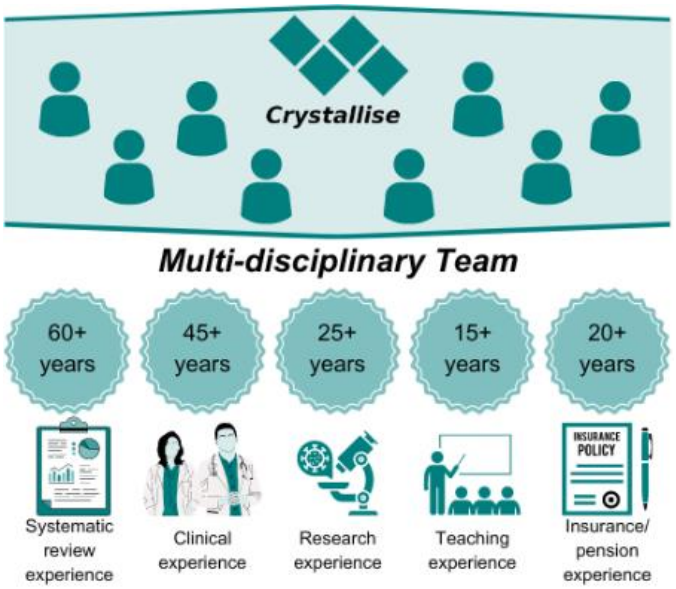

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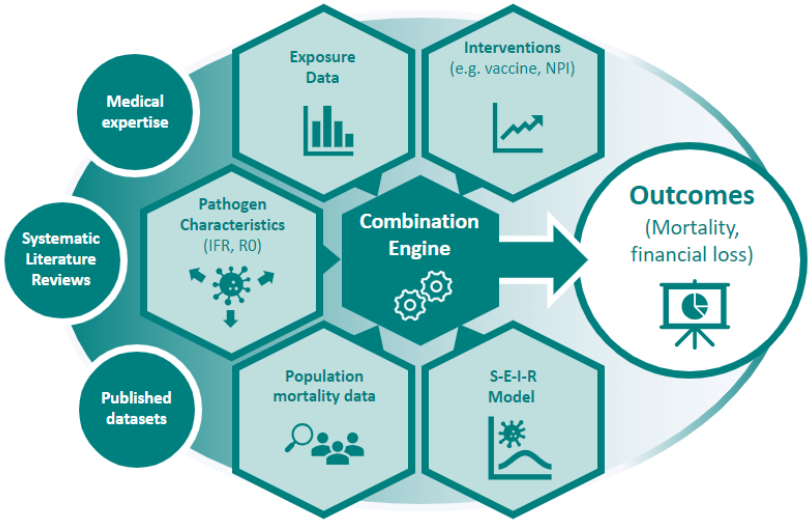

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