

Longevity Clinical Trials

Q3 2021

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Every therapeutic method used in modern medicine has passed **clinical trials**. It is the most important step of drug or therapy approval for clinical use, thus a very influential factor for the market. Longevity is an emerging field of study in the modern medical approach. Therefore most of the advances are now faced with clinical trials system. **Understanding the dynamics of Longevity therapeutics in clinical studies can grant a comprehensive analysis of the market, which can be used for its improvement.**

This analytical case study contains an **unrivaled database** that offers a deeper look at the organizations, investors, and R&D facilities that are leading in terms of the number and quality of clinical trials undertaken. **Notable trials and corporations are meticulously studied and assessed. Each stage of the trial is investigated individually.** Industry meta-analysis gives unique forecasts on market trends. Companies' classification and evaluation provide insight into probable future market force distribution. Furthermore, in-depth research findings give an overview of product trends and treatment method dynamics.

Clinical trials are an ever-expanding branch of scientific investigation. Despite the fact that the majority of them do not provide great outcomes, their paradigm underpins the whole area of contemporary medicines. Recently, more and more inventive methods of conducting research in this sector have emerged, perhaps leading to a restructuring of the approach of the trial. **This analytical case study provide insights for familiarization with clinical trials present state and longevity trials role in it.**

Approach of the Report

Database

500
Companies

300
Investors

100
R&D Centers

The database was formed based on:

- the **identification of companies and R&D centers** that conduct or have conducted clinical or preclinical researches;
- the **determination of investors** that contributed money to these companies.

Applied Research and Analytics Methods

Descriptive
Analysis

Mixed Data
Research

Data
Triangulation

Comparative
Analysis

Qualitative Data
Collection

Data
Filtering

Data Sources

Media Overview
(Articles and Press Releases)

Industry-Specialised
Databases

Publicly Available Sources
(Websites)

Industry Reports and
Reviews

Relying on various research methods and analytics techniques, the analytical provides a comprehensive overview of the Clinical Trials Industry. This approach has certain limitations, especially when using publicly available data sources and conducting secondary research. Aging Analytics Agency is not responsible for the quality of the secondary data presented herein; however, we do our best to eliminate the said risks using different analytics techniques and cross-checking data. Please note that we did not deliberately exclude certain companies from our analysis, nor was it due to the data-filtering method used or difficulties encountered. The main reason for their non-inclusion was incomplete or missing information in the available sources.

Executive Summary

Throughout history, discovering and creating new drugs played a crucial role in the life extension enterprise. After basic approach of clinical trial was described in 18th century, the efforts were made to refine the design and statistical approaches. These were followed by changes in regulatory and ethics milieu. Since then, clinical trials have evolved into a standardized procedure, focusing on scientific assessment of treatment efficacy and guarding the patient's safety.

This analytical case study includes an unexampled database which provides a closer look at the companies, investors, R&D centers leading by the amount and quality of clinical trials they conducted. Notable trials and companies are reviewed and analyzed precisely. Each phase of the trial is examined separately. Market meta analysis provides distinctive prognosis on market trends. Companies categorization and assessment shed insight on possible future forces distribution. In addition, deep research analysis provide overview on product tendencies and treatment approaches dynamics.

Main Features of the Analytical Case Study

Robust Market Players Database

Overview of Clinical Trials on All Phases

In-depth Review of Notable Clinical Trials

Detailed Assessment of Longevity Clinical Trials

Hallmarks of Aging within Clinical Trials

Precise Analysis of Age-associated Disease Studies

Clinical Trial Market Overview and Predictions

Longevity Clinical Trials Framework

Categorization of companies is **supported by literature data** regarding hallmarks of aging and age-related diseases. In addition to most significant vectors of study, **developing sectors such as research outsourcing** with *in silico* approaches were distinguished. Thus, framework not only bring **comprehensive view on market** but also **sustains relevance in advance to development** of technologies and research approaches.

By Research Field

Altered
Signaling

Cell
Senescence

Genomic and
Epigenomic Instability

Longevity

Loss of
Proteostasis

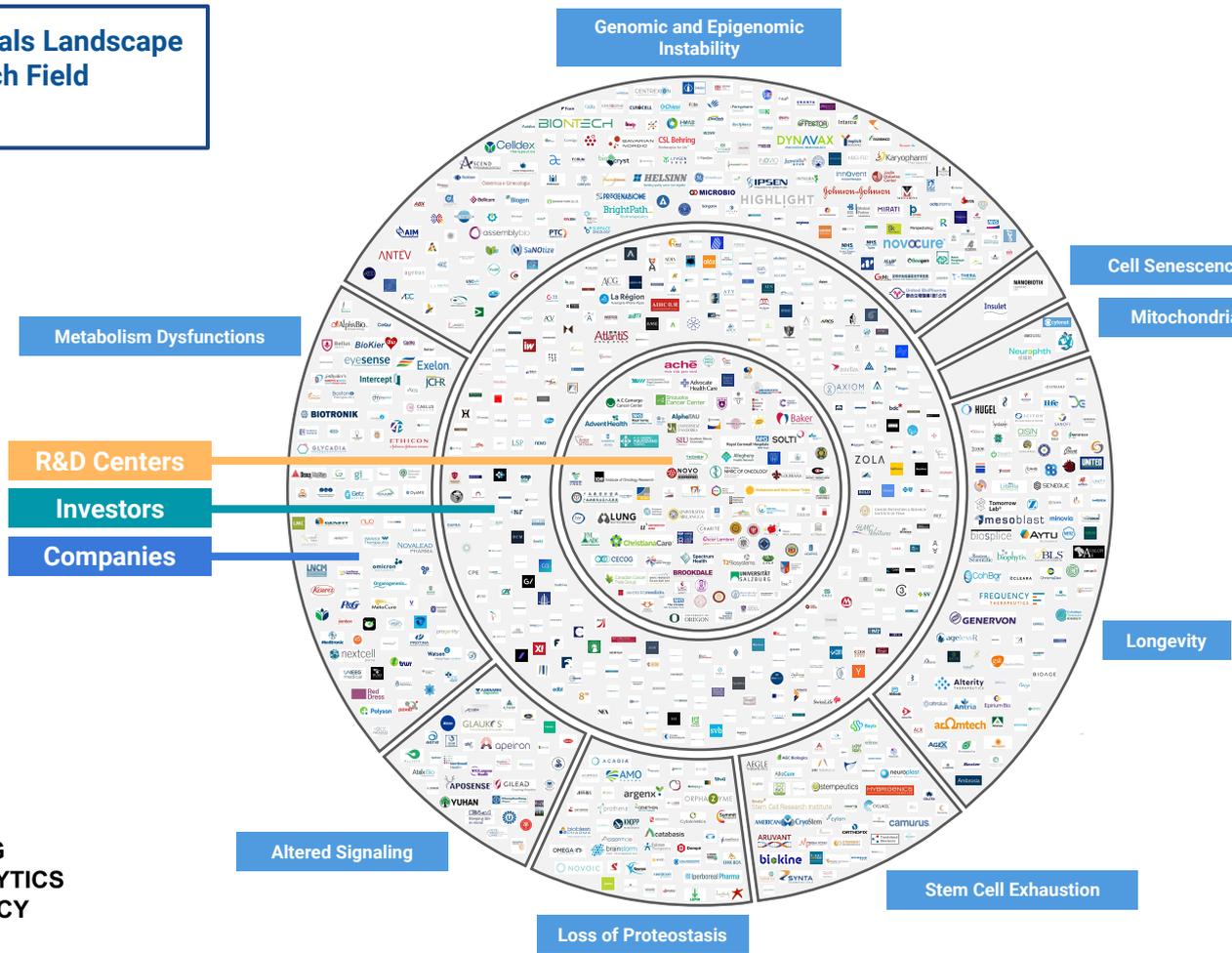
Metabolism
Dysfunctions

Mitochondrial
Disorders

Stem Cell
Exhaustion

Clinical Trials Landscape by Research Field Q3 2021

Companies – 500
Investors – 300
R&D Centers – 100



100 Leading Longevity Companies by Amount of Clinical Trials*

| | | | | | |
|----|-----------------------|----|----------------------|----|------------------------|
| 1 | AB-BIOTICS | 12 | Ambrosia | 23 | Bioenergy Life Science |
| 2 | Abbott | 13 | Aromtech | 24 | Biolab |
| 3 | Adicet Bio | 14 | Athersys | 25 | Biophytis |
| 4 | Advancells | 15 | Atropos Therapeutics | 26 | Bioquark |
| 5 | AgelessRX | 16 | Attralus | 27 | Biosplice |
| 6 | AgeX Therapeutics | 17 | Avalon AI | 28 | BioViva Science |
| 7 | Alector | 18 | Aytu Consumer Health | 29 | Boston Scientific |
| 8 | Alterity Therapeutics | 19 | Bausch Health | 30 | Calico Labs |
| 9 | ALX Oncology | 20 | Baxter International | 31 | Cerus Corporation |
| 10 | Alzheon | 21 | Bellus Health | 32 | ChromaDex |
| 11 | Amazentis | 22 | BioAge | 33 | Cleara Biotech |

100 Leading Longevity Companies by Amount of Clinical Trials*

| | | | | | |
|----|-----------------------------|----|--------------------|----|---------------------------|
| 34 | CohBar | 45 | Genome Protection | 56 | Juvenescence |
| 35 | ConvaTec | 46 | GenSight Biologics | 57 | Leucadia Therapeutics |
| 36 | Covalent Biosciences | 47 | GlaxoSmithKline | 58 | Libella Gene Therapeutics |
| 37 | CytoMed | 48 | Grifols | 59 | Life Biosciences |
| 38 | Denali Therapeutics | 49 | Healeon | 60 | Lineage Cell Therapeutics |
| 39 | Edifice Health | 50 | Hugel | 61 | Longeveron |
| 40 | Elevian | 51 | Humacyte | 62 | LyGenesis |
| 41 | Elminda | 52 | Human Longevity | 63 | MacroGenics |
| 42 | Epirium Bio | 53 | Ichor Therapeutics | 64 | Merck |
| 43 | Frequency Therapeutics | 54 | Innovaderm | 65 | MerzAesthetic |
| 44 | Genervon Biopharmaceuticals | 55 | Intervene Immune | 66 | Mesoblast |

100 Leading Longevity Companies by Amount of Clinical Trials*

| | | | | | |
|----|-----------------------|----|-------------------------|-----|--|
| 67 | Minovia Therapeutics | 78 | Revance Therapeutics | 89 | Symbioken |
| 68 | Mitotech | 79 | Revel Pharmaceuticals | 90 | Telocyte |
| 69 | Neuraly | 80 | ROKIT Healthcare | 91 | Telomere Diagnostics |
| 70 | Novartis | 81 | Sanofi | 92 | The Center for Applied Health Sciences |
| 71 | Nuritas | 82 | Scholar Rock | 93 | Tomorrowlabs |
| 72 | Oisin Biotechnologies | 83 | Sciton | 94 | Turn.Bio |
| 73 | Organovo | 84 | Seneque | 95 | Underdog Pharmaceuticals |
| 74 | Proclara Biosciences | 85 | SENISCA | 96 | United Laboratories |
| 75 | Prolacta Bioscience | 86 | Silence Therapeutics | 97 | UNITY |
| 76 | ProRelix Research | 87 | SIWA Therapeutics | 98 | veMico |
| 77 | Retrotope | 88 | Stealth BioTherapeutics | 99 | Yumanity Therapeutics |
| | | | | 100 | Zimmer Biomet |

Clinical Trials General Overview

Q3 2021



Concept of Preclinical Developments

The **preclinical study** is a stage of drug development that precedes clinical trials. It is necessary because there is a need to study the potential toxicity of a substance (or a device) before clinical trials.

The main goal of preclinical development is to **test different characteristics of a potential drug:** pharmacodynamics and pharmacokinetics, ADME (absorption, distribution, metabolism, excretion), and safe dosage for human testing.

There are two types of preclinical studies: *in vitro* and *in vivo*. ***In vitro*** means that biological agents, such as proteins, enzymes, and cells, are outside of their normal biologic context. It is also called "test-tube experiments" because the experiment is conducted in the lab. ***In vivo*** means that an experiment is conducted on the whole living system (animal tests).

Types of Preclinical Developments

| Type | Characteristic |
|---------------------|---|
| Screening | Presence or absence of certain phenomena |
| Isolated organs | Testing effect on specific organs |
| Bacterial cultures | Mostly testing microbiome reaction |
| Animal models | Modeling drug activity in living animals |
| General observation | Search for any hidden effects |
| Pharmacodynamics | Determination of mechanisms of action |
| Confirmatory tests | Milestone tests to pass different phases of trial |
| Pharmacokinetics | Studies of chemical metabolism of the drug inside an organism |
| Quantitative tests | Estimate dose-response relationship |
| Toxicity tests | Determine the toxic effects of a drug |

Concept of Clinical Trials

Clinical trials are experiments that do as a part of clinical research that **determines the safety and efficacy of new medications**, healthcare devices, diagnostic products, or behavioral interventions.

The first step of a drug trial is preclinical development, but it can not give 100% reliable information about pharmacokinetics, pharmacodynamics, and toxicity for people. Scientists can receive only approximate conclusions from their preclinical research. That is why they **need to do human experiments**.

Also, clinical trials are separated into phases. Three main phases are obligate - phases **I, II and III**. Two phases are additional (phase 0 and IV).

There are two classifications of clinical trials: **observational and interventional** studies. Observational study means that the investigators only observe the subjects and measure their outcomes but don't interfere or manage the process. Interventional study means that the investigators give the research subjects an experimental drug or a medical device. Then the researchers assess how the subjects' health changes.

Phases of Clinical Trials

| Number of Phase | Purpose | Group Sizes |
|-----------------|--|--------------------|
| Phase 0 | Pharmacokinetics and pharmacodynamics | 10-15 patients |
| Phase I | Toxicity and safety | 20-100 patients |
| Phase IIa | Optimal dosage with minimum side effects | 50-300 patients |
| Phase IIb | Preliminary efficacy of the drug in comparison with placebo | 50-300 patients |
| Phase III | Efficacy of the drug in comparison with standard treatment | 300-3000+ patients |
| Phase IV | Pharmacovigilance and technical support of a drug, addition purposes | - |

Longevity and Clinical Trials

Modern-day approaches to clinical trials were first established in the 1930s. This fact itself indicates that those approaches should be reviewed and changed. Due to active market expansion and technological progress quantity of emerging trials is growing every year. But the success ratio of traditional clinical trials has begun to decline gradually, no longer **exceeding 8-10%**, while the **failure ratio raises to 92%**. If the recent trend in clinical trial success is preserved, their financial profits will risk plateauing.

This analytical case study will show that **there are vanishingly few clinically validated drugs that reliably extend healthy human longevity**. According to prediction, the success rate of relevant drugs from mice to humans is 10% in BioTechnology in general. A mere 1% in Longevity-related subsectors means that **only 1% of Longevity-relevant clinical trials will succeed in humans**. It turns out that the overall approach to clinical trials is itself a significant limiting factor in BioTech and Longevity in particular.

Recent discoveries in the fields of cell and molecular biology brought some insights into the process of aging. Partial understanding of processes of aging opened room for extensive development of potential drugs to maintain Longevity.

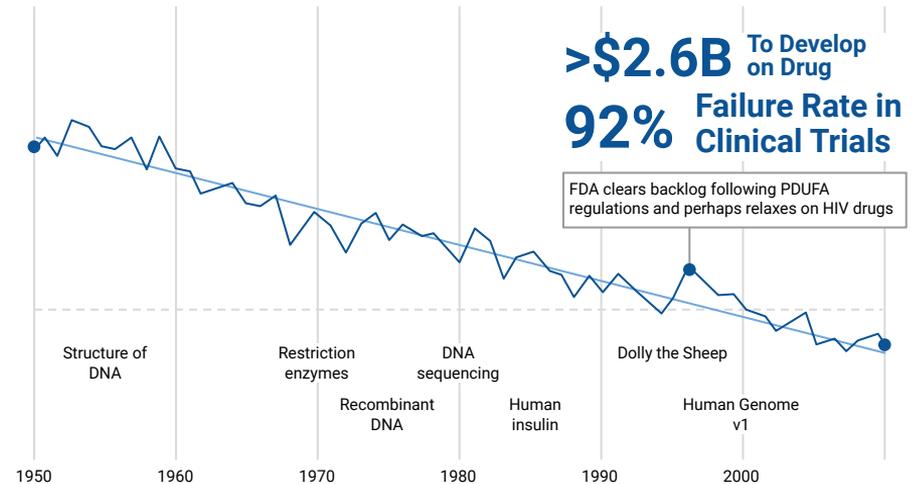
Modern gerontology research aims to **slow down** the fundamental biological processes that accompany or cause aging. These processes include but are not limited to cell aging, impaired cellular energy regulation, mitochondrial dysfunction, age-related stress resistance, and impaired proteostasis.

Source: Deep Knowledge Analytics

Aging Analytics Agency

Pharma Efficiency is Declining Steadily

MNEs per \$B R&D Spent (Inflation Adjusted)



Note: Dynamics of pharma clinical trials can be effectively used as reference for Longevity clinical trials efficiency.

The Hallmarks of Aging

Genomic Instability

Aging can be the consequence of increased DNA damage accumulation. This is due to physical, chemical, and biological agents, as well as DNA replication errors, spontaneous hydrolytic reactions, and reactive oxygen species (ROS).

Telomere Attrition

Telomeres are the chromosomal regions located on the ends of chromosomes. They tend to become increasingly shorter after each DNA replication. When this sequence ends, the cell dies. Telomerase deficiency in humans is associated with age-related diseases.

Epigenetic Alteration

Epigenetic changes involve alterations in DNA methylation, post-translational modification of histones, and chromatin remodeling. It can lead to abnormal function of cell.

Loss of Proteostasis

Proteostasis involves mechanisms for the stabilization of correctly folded proteins, as well as mechanisms for the degradation of abnormal proteins. These processes tend to change during aging.

Deregulated Nutrient Sensing

Nutrient sensing includes trophic and bioenergetic pathways, such as insulin and IGF-1, signaling pathways, and other systems (mTOR, AMPK, and sirtuins).

Mitochondrial Dysfunction

There is a noticeable reduction in ATP generation and increased electron leakage in the respiratory chain caused by aging. It is associated with mitochondrial damage.

Cellular Senescence

Cellular senescence can be defined as a stable arrest of the cell cycle. The accumulation of senescent cells in aged tissues can lead to age-related disease progression.

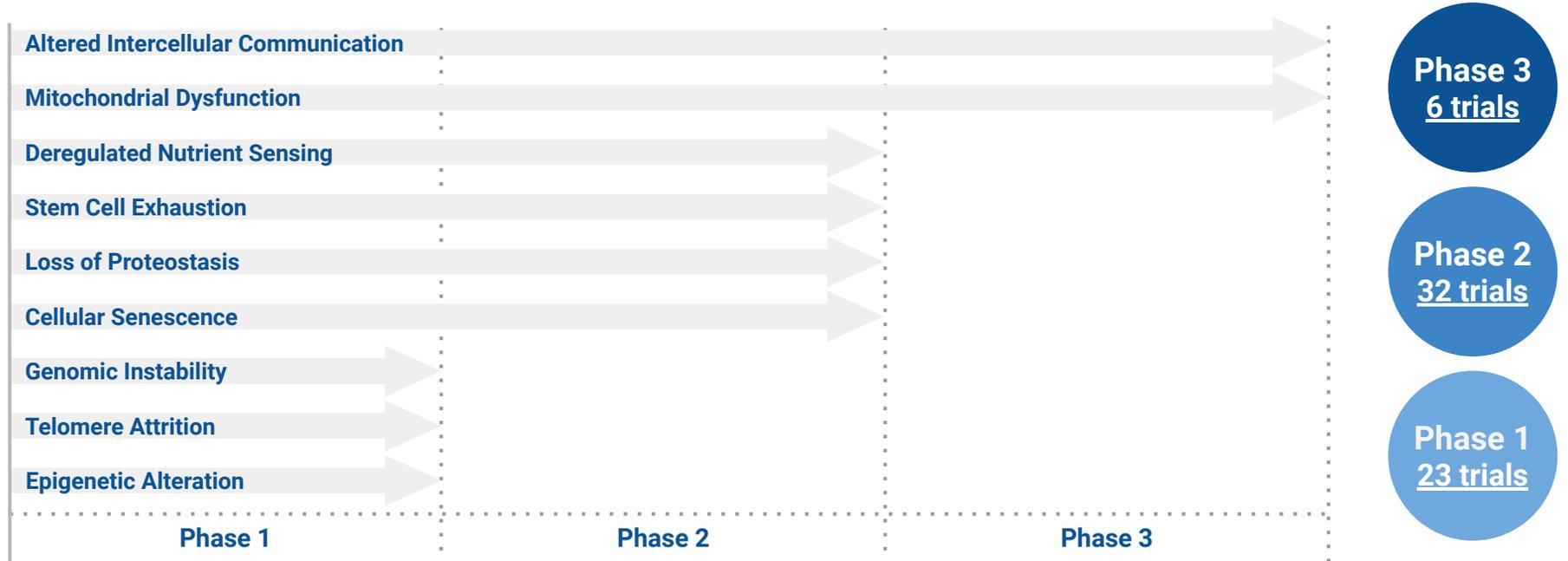
Stem Cell Exhaustion

Stem cells are cells from which all other cells with specialized functions are generated. There is a substantial decrease in the number of stem cells during life. Recent studies suggest that stem cell rejuvenation may reverse the aging phenotype.

Altered Intercellular Communication

Neurohormonal signaling tends to be deregulated in aging as inflammatory reactions increase, while immunosurveillance against pathogens and premalignant cells declines.

The Hallmarks of Aging Targets in the Clinical Trials



Note: modern attitude to clinical trials is partially conservative, some companies do not disclose information regarding their research to fortify their market position. That is why any information database is not complete. This analytical case study is based on a database consisting of all publicly open trials. Respectively, the information represented in this graph is based on this database as of Q3 2021 and will be developed in the second iteration of the project.

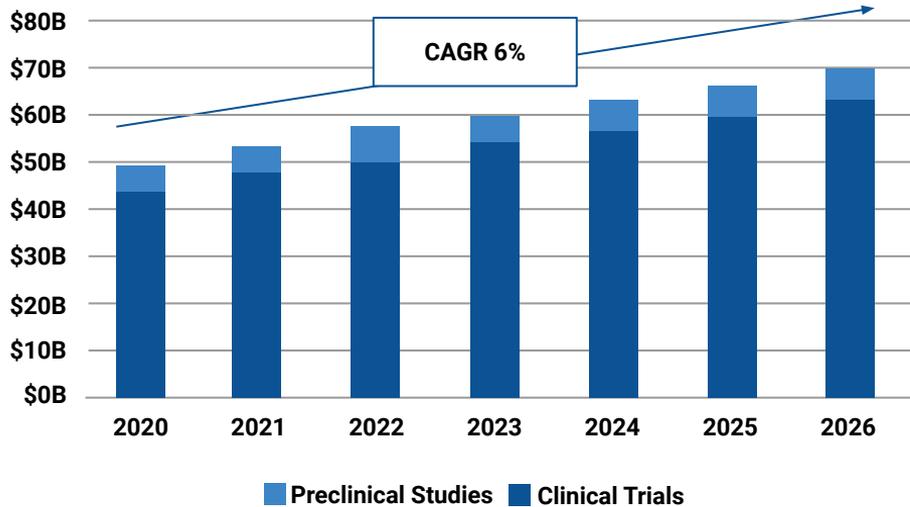
Clinical Trials Market Overview

Q3 2021



Clinical Trials Market at a Glance

Preclinical Studies and Clinical Trials Market Size, 2020-2026



The global **Preclinical Studies and Clinical Trials Market Size** accounted for **\$48.8B in 2020** and is projected to grow an average **CAGR of 6%** from 2020 till 2026 to reach **\$70.5B**. Despite increasing interest in recent years, the industry remains underestimated and has high growth potential.

The key market drivers include **rising life expectancy and disposable income; increased R&D spending of new drugs** by pharmaceutical companies. Due to high competition, companies are looking to **diversify their product portfolio with specialty drugs**. Additional **demand for clinical and preclinical services arises** because more pharmaceutical companies outsource large parts of R&D, primarily to clinical research organizations, to reduce costs.

3.4%

Global GDP Growth
in 2021

3.7%

Global Spending Growth on
Pharma R&D in 2021

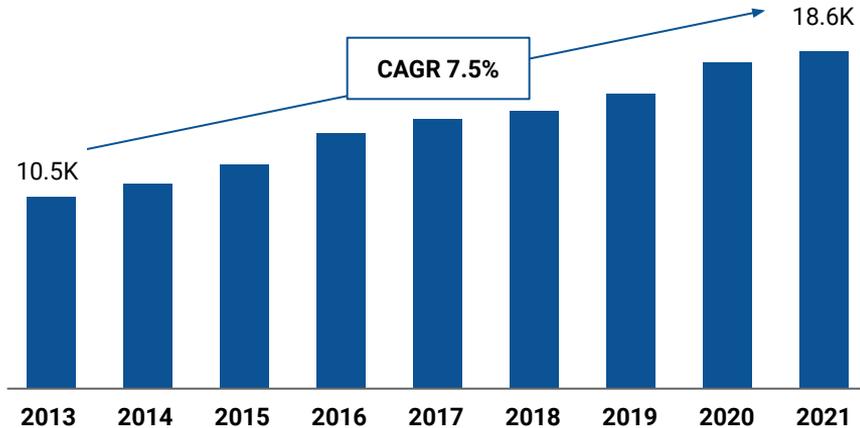
0.24%

Life Expectancy
Growth in 2021

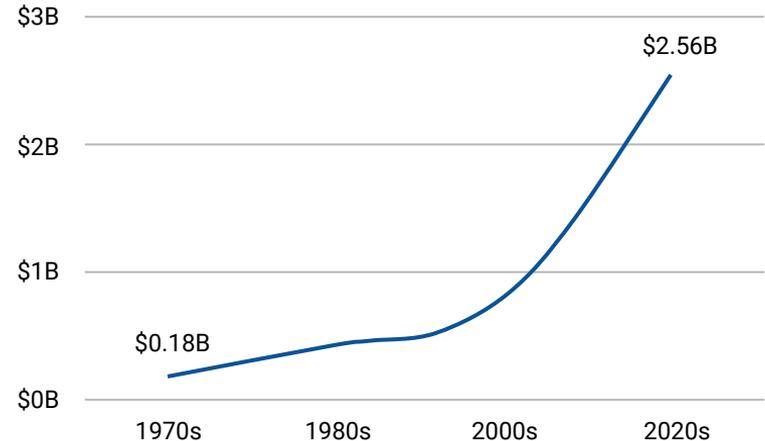
Sources: Grand View Research, Statista, IMF, Macrotrends

Clinical Trials Market at a Glance

Number of Drugs in the R&D Pipeline Worldwide, 2013-2021



Cost of Development Drugs in USA, 1970-2021



The development of a new innovative product requires significant resources and time. After the initial research, drug manufacturers must conduct a series of trials to obtain approval. The increase in the number of drugs in development **increases the need for more preclinical studies and clinical trials**. The cost in the 2020s showed that **\$2.5-2.6B for development** to include approximate average out-of-pocket cost of **\$1.4B and time costs** (the expected returns that investors forego while a drug is in development) of **\$1.2B**. In addition, the estimated cost of post-approval research and development of **\$0.31B** boosts the **full product lifecycle cost** per approved drug close to **\$3B**.

Clinical Trials Market at a Glance

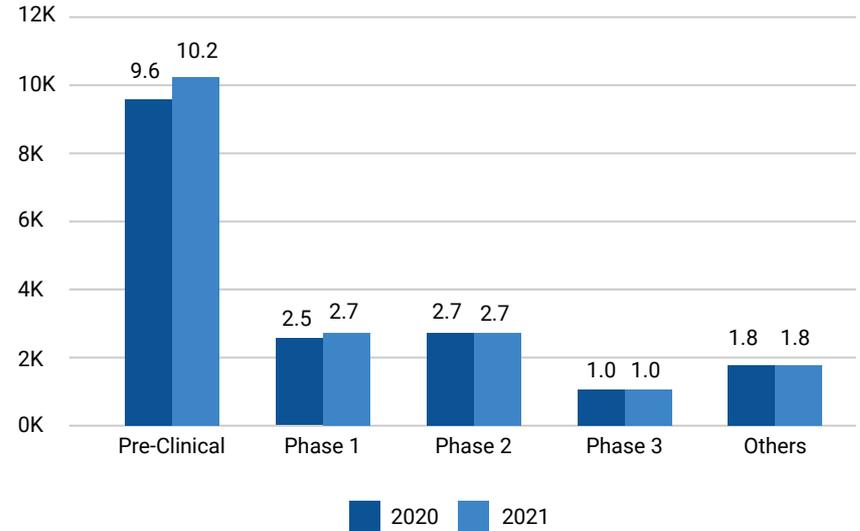
Preclinical studies involve extensive preclinical studies that yield preliminary efficacy, toxicity, pharmacokinetic, and safety information, testing by using test tubes, cell culture, or animals.

The global **Preclinical Studies Market Size** accounted for **\$5B in 2021** and is projected to grow an average **CAGR of 8.1%** from 2020 till 2026 to reach **\$7.4B**.

In 2016 USA passed the 21st Century Cures Act, which accelerated the **approval process for advanced drugs and medical devices**, which accelerated the growth of the market, where the USA share in 2020 was **47.7%**. The largest share of the global market income in 2020 was occupied by **toxicological preclinical studies** with a share of **61.1%** due to a rise in the outsourcing of noncore preclinical CRO studies and high adoption in toxicology tests.

Sources: Grand View Research, Statista

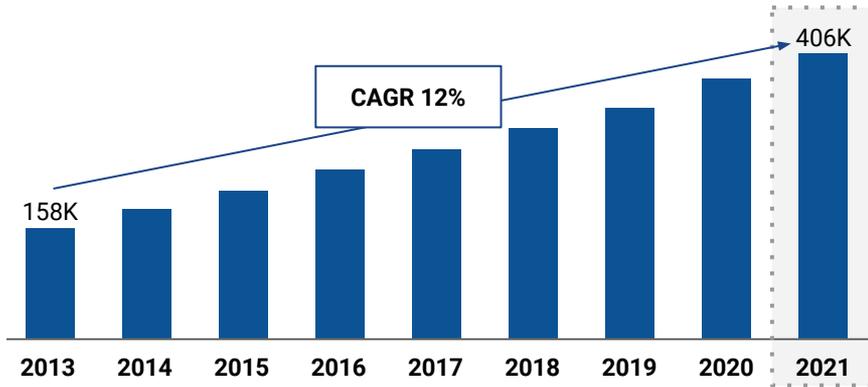
Number of Drugs in the R&D Pipeline Worldwide, 2020-2021



Note: Others - trials that have alternative approach to studies due to local policies.

Clinical Trials Market Overview

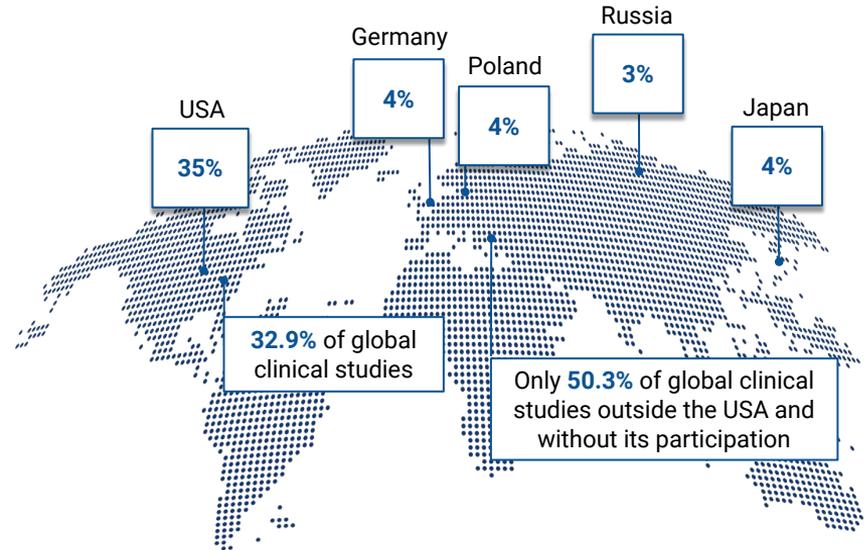
Total Number of Registered Clinical Trials Worldwide, 2013-2021



Clinical trials are the main part of the drug development process, because they determine the safety and efficacy of the drugs effect on the human body. The global **Clinical Market Size** accounted for **\$47.4B in 2021** and is projected to grow an average **CAGR of 5.9%** from 2020 till 2026. The **complexity** of conducting clinical trials in U.S. **has grown by 61%** from 2001 to 2015, which increases the demand for specialized clinical trials companies.

Sources: Grand View Research, Statista, ClinicalTrials.gov, Research Gate

Top-5 Clinical Trials Participants by Country in 2021



32.9% of global clinical studies

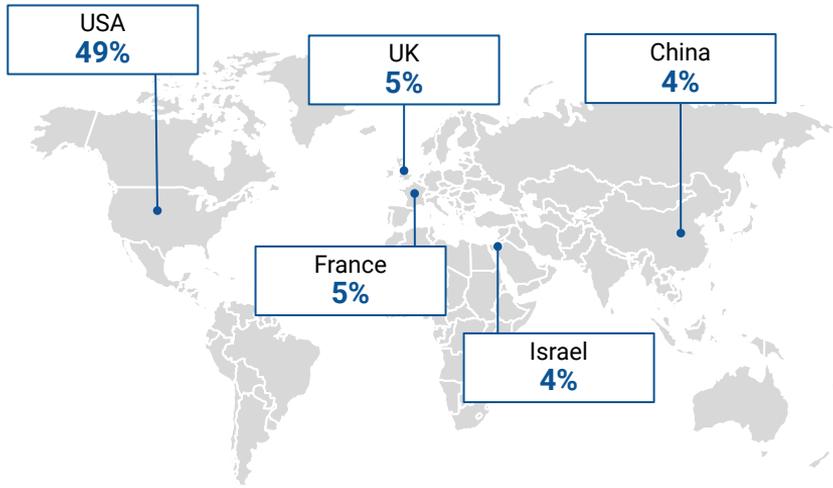
Only 50.3% of global clinical studies outside the USA and without its participation

Probability of Success for Drugs in the USA in Different Development Clinical Trial Phase

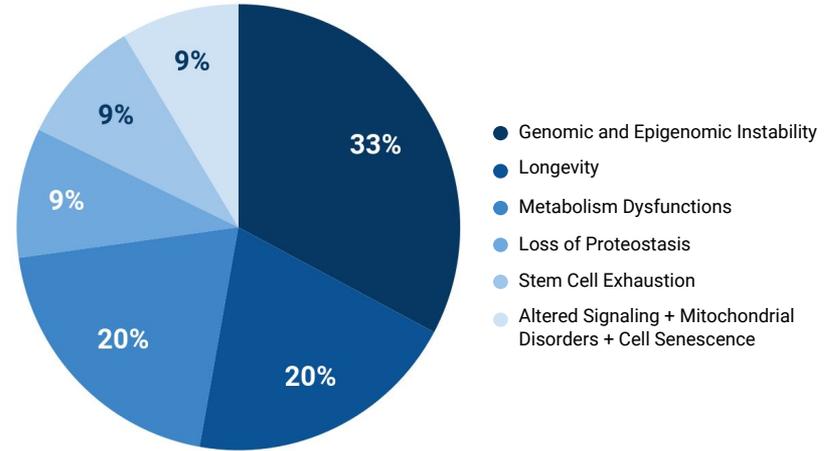


Clinical Trials Market Overview

Distribution of Companies by Country, %



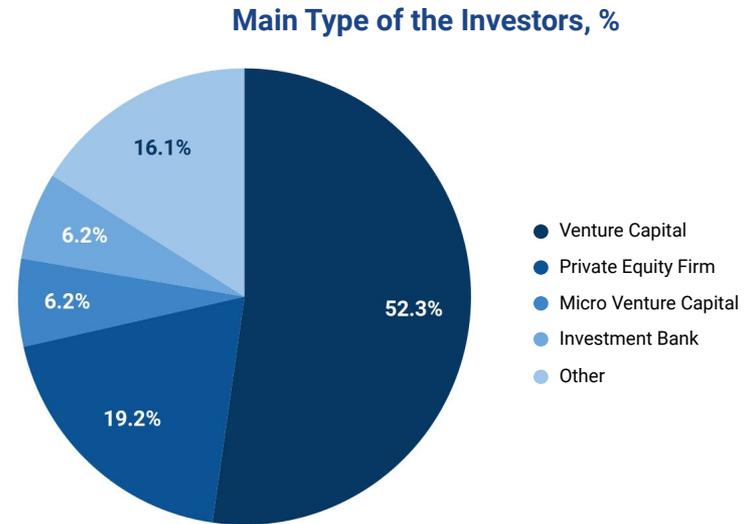
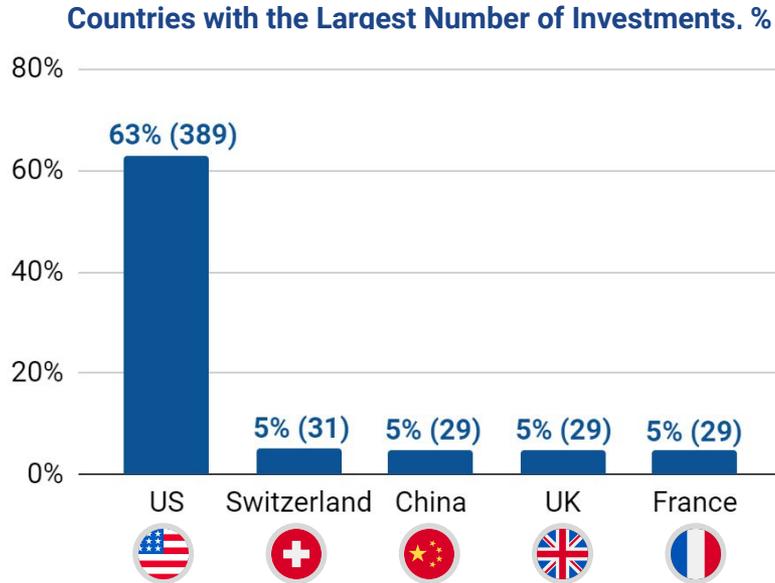
Distribution of Clinical Trials by Category, %



The **vast majority** of companies that conduct Clinical Trials is located in the **United States** and accounts for **49%** of the whole range of analyzed companies. The United States is followed by the **European region**, particularly by the **United Kingdom** and **France** with the total companies amount equal to **5%** of all companies in **both** of the countries.

The main domains in which Clinical Trials are being conducted are **Genomic and epigenomic instability**, **Longevity** and **Metabolism dysfunctions** which account for **33%**, **20%** and **20%** of all Clinical Trials **respectively**.

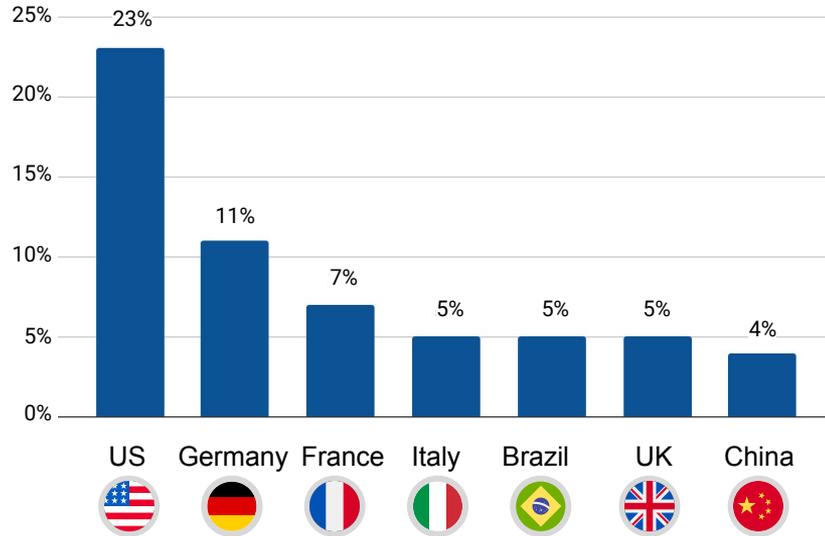
Clinical Trials Market Overview



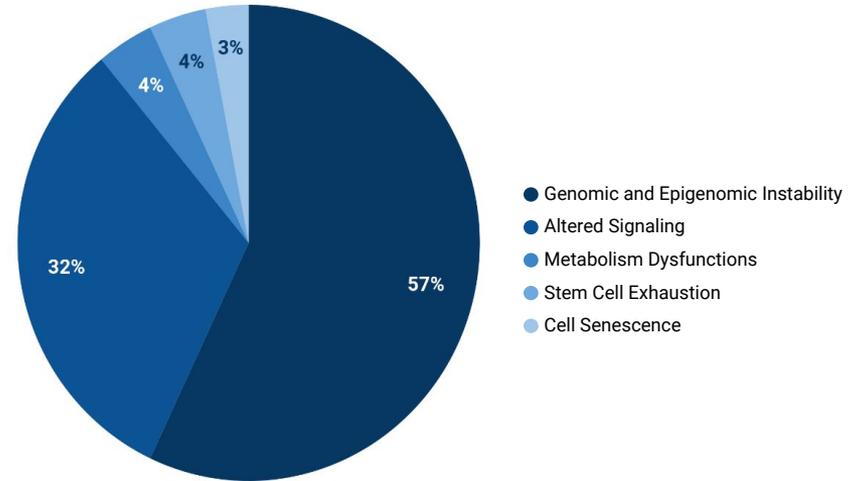
The main part of the investments in Clinical Trials was made by investors from the **United States** and accounts for **63%** of the total investments amount. Investors from **Switzerland, China, United Kingdom** and **France** follow the United States with **5%** of total investments made in each country. Most of the investors are **Venture Capitals** which constitute more than half of all Investors (**52.3%**). The other main types of Investors are **Private Equity Firm (19.2%)**, **Micro Venture Capital (6.2%)** and **Investments Bank (6.2%)**.

Clinical Trials Market Overview

Countries with the Largest Number of R&D Centers, %



Distribution of R&D Centers by Categories, %

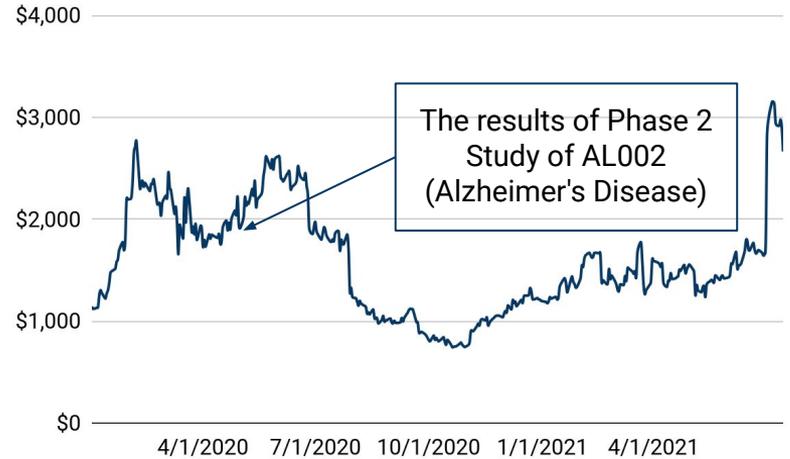


More than a fifth of leading R&D centers that conduct clinical trials on Longevity-related topics are situated **in the United States**. Around **27%** of R&D centers are allocated **in the European region**: 11% - in Germany, 7% - in France, and 5% each in Italy and the United Kingdom. Among the top 5 research directions, **53%** of R&D centers are engaged in the field of **Genomic and epigenomic instability**. Another **third** of centers provide studies in the field of **Altered signaling**. **Metabolism dysfunctions**, **Stem cell exhaustion**, and **Cell senescence** are developed by **4%**, **4%**, and **3%** of centers **respectively**.

Source: Aging Analytics Agency analysis

Alector is a clinical-stage biopharmaceutical company, develops therapies for the treatment of neurodegeneration diseases. Its products include **AL001**, that is in **Phase 2** clinical trial for the treatment of frontotemporal dementia disease and **AL101** that is in **Phase 1** clinical trial for the treatment of neurodegenerative diseases. The company also offers **AL002** and **AL003**, which are in **Phase 1b** clinical trials for the treatment of Alzheimer's disease.

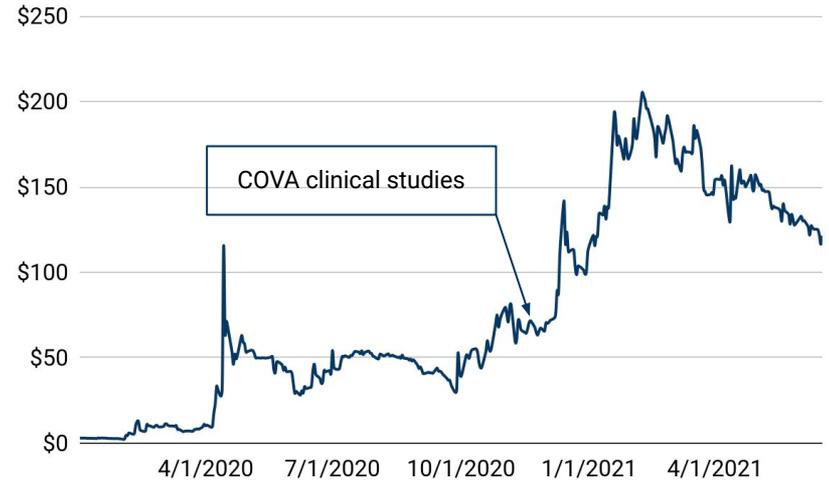
On the following chart, the market capitalization of **Alector** is depicted in \$M. The company's financial underperformance led to a significant capitalization decline in Q3 2020. The results of a **Phase 2** study of **AL002** in participants with early Alzheimer's Disease were perceived negatively by the market, which exacerbated the further decline.



Source: ClinicalTrials.gov, Koyfin

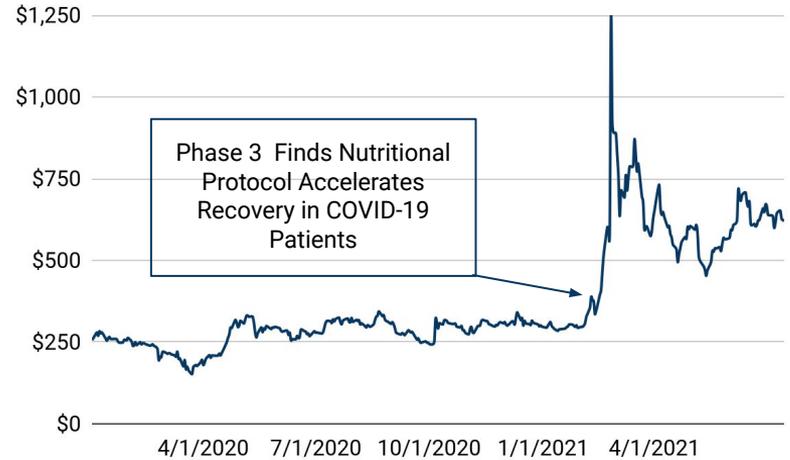
Biophytis is a clinical-stage biotechnology company, focuses on the development of therapeutics that slow the degenerative processes and improve functional outcomes for patients suffering from age-related diseases. The two main medicines are **Sarconeos (BIO101)** from the treatment of neuromuscular diseases and **Macuneos (BIO201)** from the treatment of retinal diseases.

On the following chart, the market capitalization of **Biophytis** is depicted in \$M. Great capitalization performance of the company is obtained due to the good financial and medical pipeline performance, including success in the COVA clinical studies, additionally, Biophytis receives \$1.16M DeepTech Funding from BPI France for the Development of Macuneos (BIO201) in Dry AMD.



ChromaDex operates as a bioscience company focusing on healthy aging. The company operates through three segments: Consumer products; Ingredients; and Analytical Reference Standards and Services.

On the following chart, the market capitalization of **ChromaDex** is depicted as \$M. When the company launched results “New **Phase 3** Clinical Study Finds Nutritional Protocol Including **Nicotinamide Riboside Accelerates Recovery in Mild-to-Moderate COVID-19 Patients**” the market overreacted during the first days, but after correction the capitalisation doubled thanks to this release.



CohBar is a clinical stage biotechnology company, engages in the research and development of mitochondria based therapeutics (MBTs) for the treatment of chronic and age-related diseases. Its lead MBT candidate is CB4211 in Phase Ib stage of a Phase Ia/Ib clinical trial. The company's preclinical programs include CB5138 analogs for fibrotic diseases, CB5064 analogs for COVID-19 associated ARDS, MBT5 analogs for CXCR4-related cancer and orphan diseases, and MBT3 analogs for cancer immunotherapy.

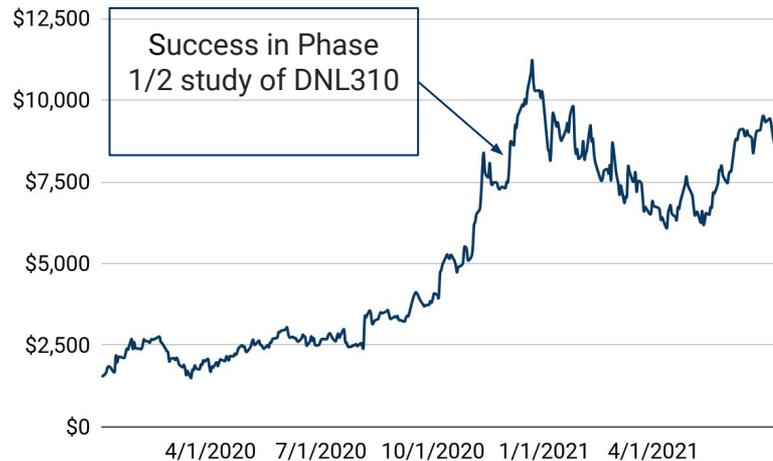
On the following chart, the market capitalization of **CohBar** is depicted in \$M. The spikes were gained due to the fact that the company has completed dosing in its Phase 1b study evaluating CB4211 as potential treatments for NASH and obesity.



Source: ClinicalTrials.gov, Koyfin

Denali Therapeutics is a biopharmaceutical company, discovers and develops therapeutic candidates for neurodegenerative diseases in the United States. The company offers leucine-rich repeat kinase 2 (**LRRK2**) inhibitor product candidates, including **DNL201** that has completed **Phase 1b**, and **DNL151**, which are in **Phase 1** and **Phase 1b**.

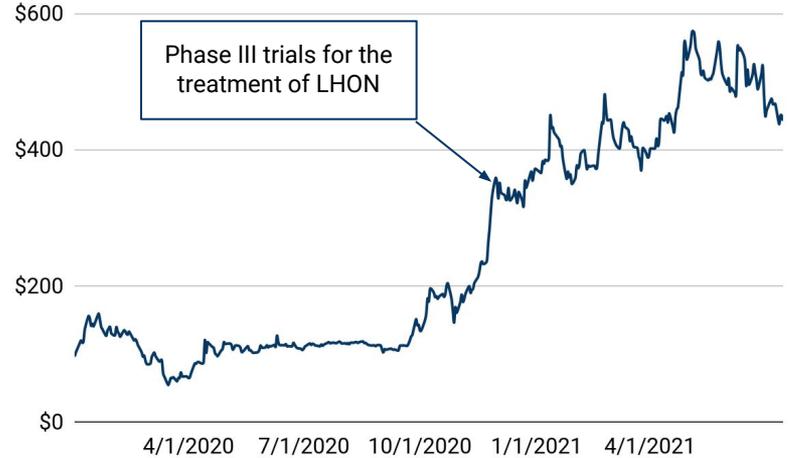
On the following chart the market capitalization of Denali Therapeutics is depicted in \$M. The significant spike in the capitalization of the company is gained due to the both strong financial performance in the past year and success in **Phase 1/2** study of **DNL310** in patients with Hunter syndrome (MPS II) and **Phase 1b** study of **DNL151**.



Source: ClinicalTrials.gov, Koyfin

GenSight Biologics is a clinical-stage biotechnology company, engages in the discovery and development of therapies for mitochondrial and neurodegenerative diseases of the eye and central nervous system.

On the following chart, the market capitalization of **GenSight Biologics** is depicted in \$M. The skyrocketing capitalization of the company is based on the good medical pipeline performance, namely **Phase III** trials of LUMEVOQ® (GS010) for the treatment of Leber Hereditary Optic Neuropathy (LHON) are **completed**. The manufacturing process also seems to be quite stable, since the company's **CDMO** is **Thermo Fischer Scientific**.



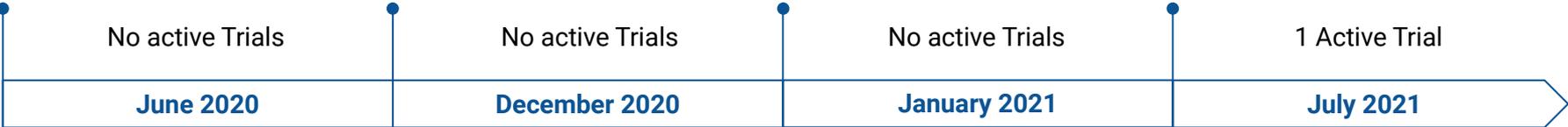
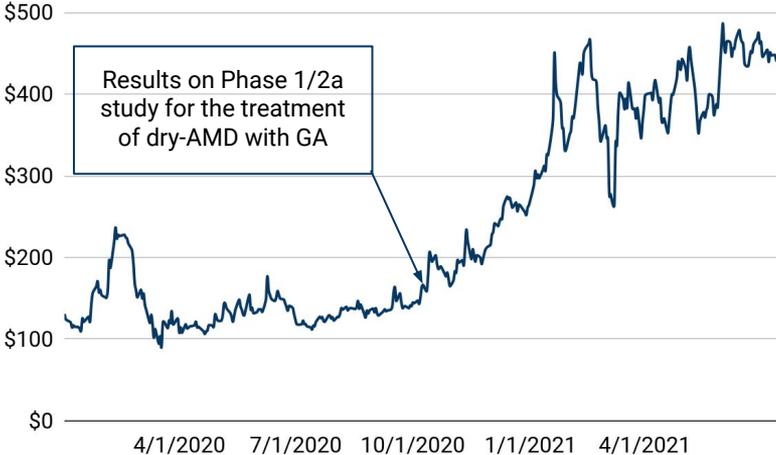
Source: ClinicalTrials.gov, Koyfin

Lineage Cell Therapeutics



Lineage Cell Therapeutics is a clinical-stage biotechnology company, focuses on developing and commercializing therapies for the treatment of degenerative diseases in the United States and internationally.

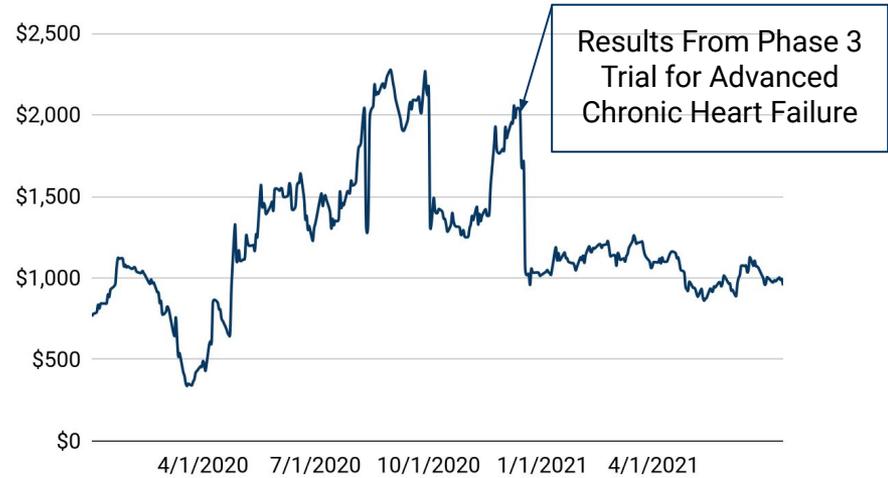
On the following chart, the market capitalization of **Lineage Cell Therapeutics** is depicted in \$M. The company has positive capitalization dynamic in 2021 based on the present positive clinical update from the ongoing **Phase 1/2a** study of OpRegen for the treatment of dry-AMD with GA; the company also reported **the first known finding of retinal tissue restoration** in a patient who received a retinal pigment epithelium (RPE) cell transplant continues to demonstrate areas of retinal restoration as of their last assessment, approximately 3 years after treatment.



Source: ClinicalTrials.gov, Koyfin

Mesoblast Limited is a biopharmaceutical company, develops and commercializes allogeneic cellular medicines. The company offers products in the areas of cardiovascular, spine orthopedic disorder, oncology, hematology, and immune-mediated and inflammatory diseases.

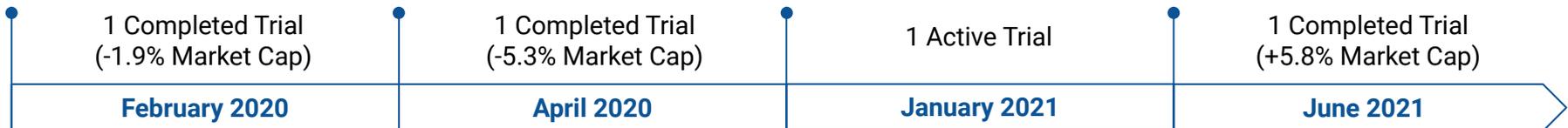
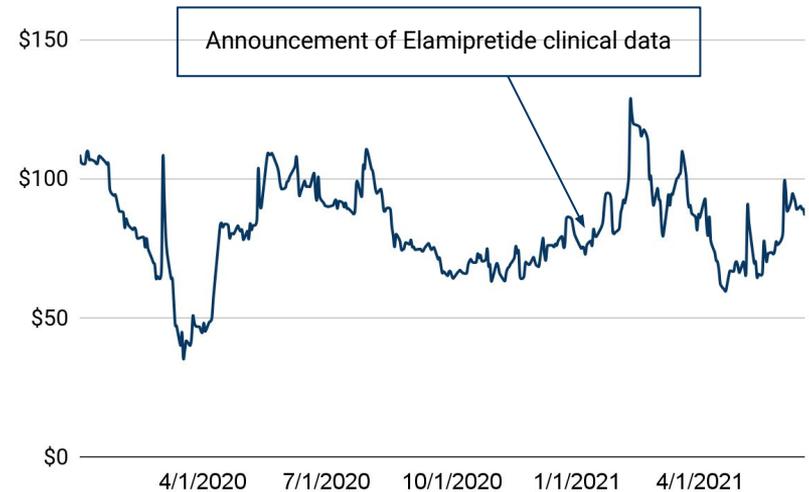
On the following chart, the market capitalization of **Mesoblast** is depicted in \$M. In December 2020 **Mesoblast Ltd.** saw its stock drop on the news that its allogeneic mesenchymal cell therapy, **rexlemestrocel-L (Revascor)**, failed to meet the primary endpoint of a reduction in hospitalizations in its **Phase 3** advanced chronic heart failure trial.



Source: ClinicalTrials.gov, Koyfin

Stealth BioTherapeutics

Stealth BioTherapeutics (MITO) is a clinical-stage biotechnology company, focuses on the discovery, development, and commercialization of therapies for diseases involving mitochondrial dysfunction. Its lead product candidates: Elamipretide, SBT-20, SBT-272. The market capitalization of the company is depicted in \$M. **MITO** shares have fallen 26.40% over the year. However, they have moved up 9.85% at the beginning of June 2021 after the past three months' decline of market capitalization. In April 2021, the company delayed an NDA filing for elamipretide for cardiomyopathy in Barth syndrome that led to a 10% fall in capitalization. Besides that, **Stealth BioTherapeutics Corp** has reached an agreement with Morningside Ventures for Morningside to provide \$30M of additional payments to the Company during 2021, which helps to do more clinical trials.

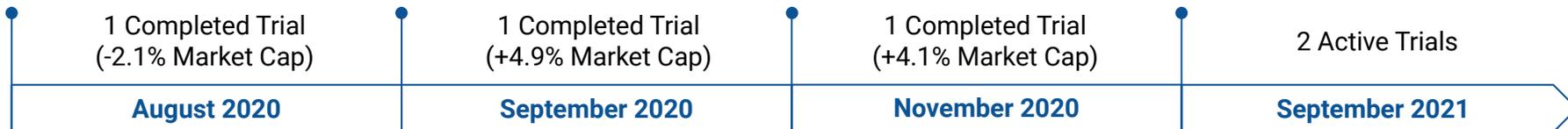
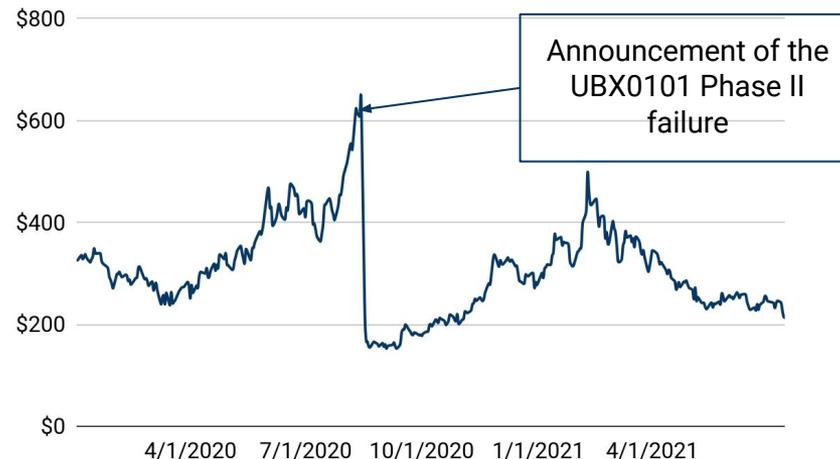


Source: ClinicalTrials.gov, Koyfin

Unity Biotechnology

Unity Biotechnology is a biotechnology company, engaged in the research and development of therapeutics to extend human healthspan. The company's lead drug candidates include **UBX0101** that is in **Phase II** clinical trial for musculoskeletal/ osteoarthritis disease, as well as Phase Ib clinical trial for moderate-to-severe osteoarthritis of the knee.

On the following chart, the market capitalization of Unity Biotechnology is depicted in \$M. A significant drop in capitalization is gained due to the **UBX0101 Phase II** failure.



Preclinical Development of Drugs for Age-related Conditions



Preclinical Development of Drugs for Age-related Conditions

In modern clinical study approach prior to testing drug or therapeutic approach on humans, researchers are obligated to complete set of preclinical studies.

That is part of research which is **focused on testing possible toxicity or sometimes therapeutic effect on models**. Preclinical studies are designed specifically to move to clinical studies.

Classical approach to conducting preclinical studies involves **animal testing**. But with development of new ways of modeling substances interactions and reactions some of studies could be moved to computer modeling in the future. This vector of research is currently developing, emergence of companies which digitally assist with modeling proves this tendency.

The most common conditions modeled at present moment are: **Neurodegenerative disease, Aging of a tissue/organ, Cardiovascular disease, Bone disease**.

Study Models

| Model | Characteristics |
|---------------------------|--|
| <i>In Vitro</i> | High speed, low cost, limited to molecular level |
| Rodents | Low cost, fast, almost universal |
| Swine | Whole range of conditions, expensive, long-lasting |
| Non-human Primates | Whole range of conditions, expensive, long-lasting |
| Digital | Short term, cheap, limited to cell level |

Note: digital approach is believed to be the most time and cost effective, as well as that it is more ethical, but it is yet not approved for trial reports. Which leads to duplication of studies for different tests.

Preclinical Development of Drugs for Age-related Conditions

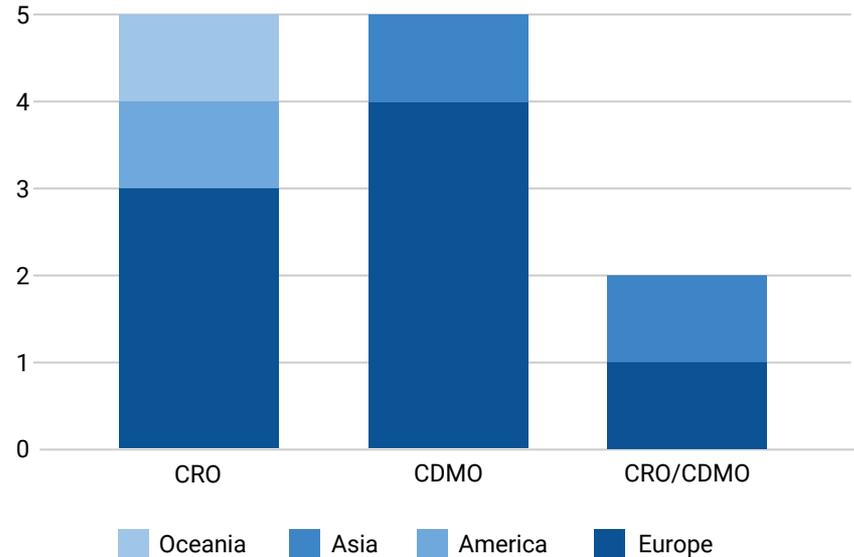
The number of **preclinical studies** is expected to grow by 6% to **10.2K** in 2021.

Research **results are presented in 4.5% of trials**. Some of results trials were indirectly associated with aging and its consequences: Hemorrhage (52.2%), Huntington's Disease (38%), IntraCerebral Hemorrhage (4.3%), Triple Negative Breast Cancer (2%), Ischemic stroke (0.7%). In addition, according to the National Library of Medicine (NIH), more than **402 direct preclinical studies related to the topic of aging** were conducted, of which 3.5% were conducted in 2021. **Most of the trials were tested on animals (98.2%)**, the rest used human blood. The studies involved **3.5K animals**, the largest proportions of which were mice (63%) and rats (23%).

Preclinical research outsourcing services are provided by **58.3% of companies**, most of which are located in the European Region (57%).

Sources: National Library of Medicine, Statista

Distribution of Main Preclinical Studies (CRO) and Clinical Trials (CDMO) Companies, Amount



Note: this graph depicts distribution of main preclinical and clinical trials companies by according to [Invesder](#).

Preclinical Development of Drugs for Age-related Conditions

The market is continuously growing but has drawbacks.

One of the main concerns in preclinical developments of aging is **distinctive evaluation of biological age**. It is the main reason diagnostics of aging is in scope of studies today.

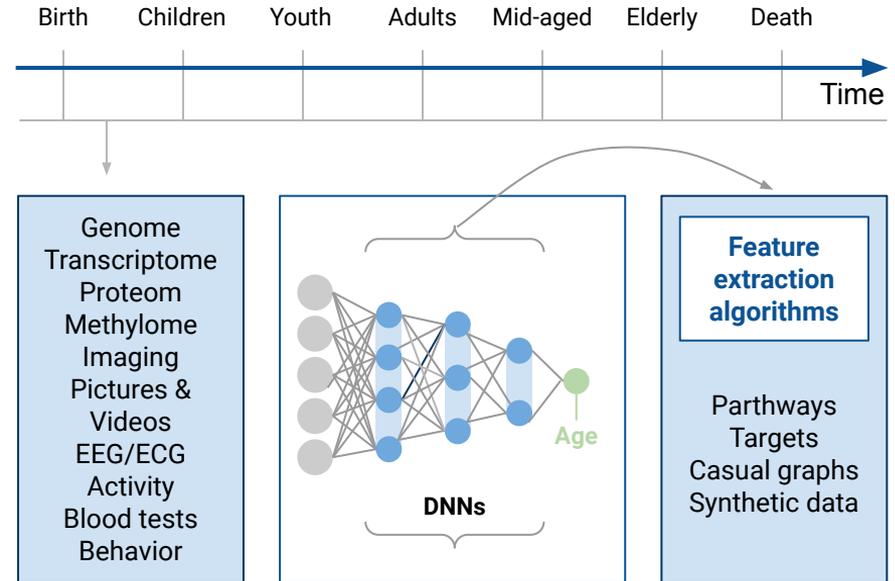
For present moment, researches are either **focused on specific modeled disease or on overall inflamaging of an organism**.

The era of personalized medicine has made it clear that both genetics and environment influence therapeutic outcome. As **mutations associated with age-related diseases are elucidated**, the development of preclinical models to mimic these genetic risk factors would be useful in intervention testing.

Today, progress in aging research is hindered by barriers associated with the **translation of basic science discoveries into the clinic**.

Sources: Ageing Research Reviews

Aging Analytics Agency



Note: training the deep neural networks on multimodal longitudinal data to predict (A) age of the individual and (B) age and health status of the individual and using the feature importance and selection approaches to infer causal relationships, pathways, and targets.

Longevity Drugs in Preclinical Development

| Company | Drug Candidate | Company | Drug Candidate |
|---|---|---|---|
|  | Enzymes which break glucosepane to restore tissue plasticity |  | GlycoSENS: destroys glucosepane crosslinks to restore movement to the structural proteins |
|  | Mitochondrial/Metabolic therapies for aging, to restore normal function of different cells |  | Cyclodextrins to fight 7-ketocholesterol and remove artery plaques which causes heart diseases |
|  | Senolytic drugs to target the pathways of aging in senescent cells, thus reduce senescence potential |  | Peptope and CAR-M immunotherapies against transthyretin amyloidosis |
|  | Senosuppressors - drugs to decrease effect of senescent cells on organism |  | USP14 inhibitors to treat Alzheimer's and Parkinson's diseases |
|  | Medicines intended to improve egg cell quality and restore fertility in women of advancing age |  | Using machine learning to help it map new genes that were not previously recorded |

Longevity Drugs in Preclinical Development

| Company | Drug Candidate | Company | Drug Candidate |
|---|---|--|---|
|  | Telomerase gene therapy - to reduce cancerogenesis, degenerate tumors | COVALENT BIOSCIENCE, Inc  <i>Nature-Made Catalytic Antibodies for Health</i> | Cardizyme destroys transthyretin amyloid (misTTR) which causes age-related heart diseases |
|  | Telomerase therapy & proprietary induced tissue regeneration (iTR) technology | COVALENT BIOSCIENCE, Inc  <i>Nature-Made Catalytic Antibodies for Health</i> | Alzyme destroys amyloid beta, a misfolded protein that forms Alzheimer's plaques |
|  | OSKM factors: epigenetic cells' reprogramming into induced pluripotent stem cells (iPSCs) by expression Yamanaka genes |  LEUCADIA Therapeutics | Arethusta promoting the flow of cerebrospinal fluid (CSF) through the brain to treat the Alzheimer's disease |
|  | OSKMLN factors: epigenetic cells' reprogramming into induced pluripotent stem cells (iPSCs) by expression Yamanaka genes |  | Medication to improve the removal of damaged or misfolded proteins that accumulate with aging |
|  | LYSOCLEAR: an enzyme which disrupts a lipofuscin |  | Klotho protein , suppressor of insulin and insulin-like growth factor 1 (IGF1) |

Longevity Drugs in Preclinical Development

| Company | Drug Candidate | Company | Drug Candidate |
|---|---|---|--|
|  | FOXO4-DRI causes apoptosis in the senescent cells |  | Epigenetic Reprogramming for tissue rejuvenation |
|  | Senolytics - therapy to remove senescent cells, lower senescence impact on organism |  | Gene apheresis to restore stem cell reserve |
|  | MitoSENS to prevent mitochondrial aging thus stabilize all cells |  | An immunotherapy for removing cancer and senescent cells |
|  | Developing a drug that restores egg cell quality and fertility |  | Gene therapy for short telomere restoration |
|  | Mitochondrial/Metabolic therapies for restoring normal functions of individual cells |  | Modulating RNA splicing to rejuvenate aged cells |
|  | The plasmid-based senolytics (SENSOlytics™) to remove senescent cells |  | Medication to restore regenerative capacity, with the potential to prevent age-related diseases |

Age-associated Disease Clinical Trials



Age-associated Disease Clinical Trials

The percentage of national **populations over age 65 has been increasing** in the last 10 years and **will continue to rise** for another 20 years due to improved life expectancies.

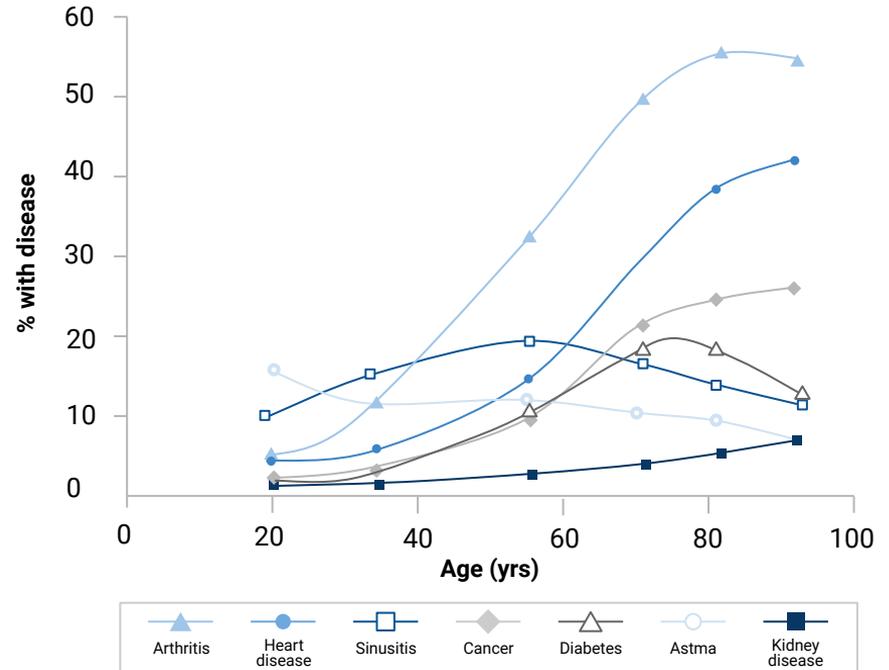
It leads to the rise of age-associated diseases frequency in population. Most of Longevity clinical trials are focused on specific problems - **certain age-associated disease**.

It is hard to focus on distinct pathologies because in the process of aging, every organ of body loses its effectiveness, but most common pathologies are in scope of clinical trials. Such groups of diseases are: **cancer, CNS conditions, diabetes, chronic pain and autoimmune reactions**.

Yet treatment of those conditions is only symptomatic due to complicated etiology.

There is no universal solution, but some therapies can help lower the risks or manifestations, such as: **senolytics, stem cell therapies, anti inflammation therapies**.

Age-associated Disease Diagnosis Ratio



Note: this graph represents frequency of age-associated disease diagnosis in population relatively to age.

Oncology

Aging is the inevitable time-dependent decline in physiological organ function and is **a major risk factor for cancer development**. Due to advances in health care, hygiene control and food availability, life expectancy is increasing and the population in most developed countries is shifting to an increasing proportion of people at a cancer susceptible age. Mechanisms of aging are also found to occur in carcinogenesis, albeit with shared or divergent end-results.

Despite considerable investment in oncological research, the rate of improvement in **cancer treatments remains frustratingly slow** and the attrition rate in anticancer drug development has reached extremely high levels. New skills are required to push the research further in terms of clinical, biological and imaging data and the decision-making process.

Source: GlobalData website

Goals of Cancer Clinical Trials

Treat Cancer

Find and Diagnose Cancer

Prevent Cancer or its Complications

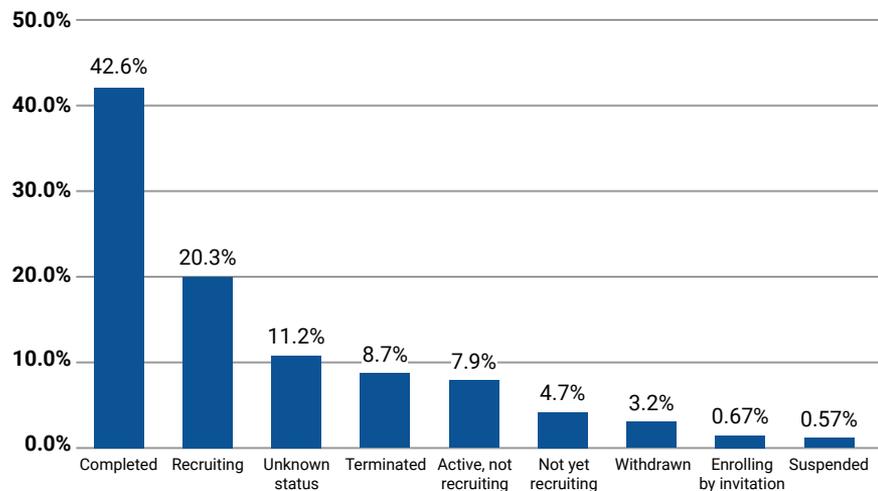
Manage Symptoms of Cancer and Side Effects from its Treatment

Improve Quality of Life for People with Cancer

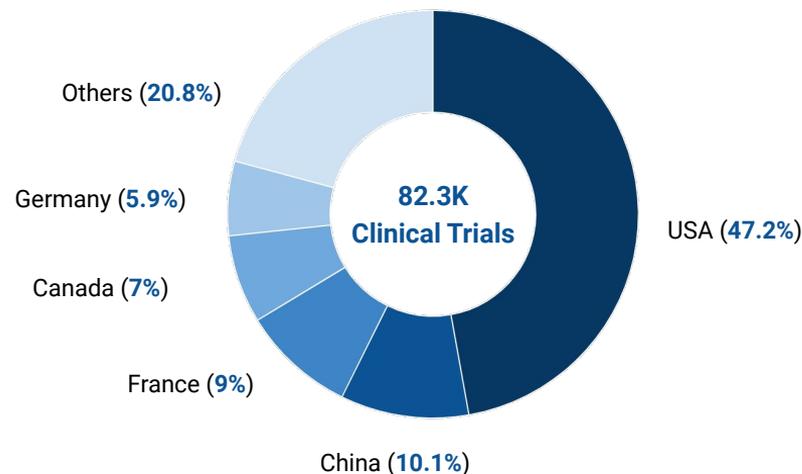
Note: four of the top seven non-marketed drugs are monoclonal antibodies, suggesting the rising interest in these agents, particularly within the oncology research space.

Oncology

Status of Clinical Trials on Oncology in Q1 2021



Top-5 Countries for Clinical Trials on Oncology in Q1 2021



The number of clinical trials of oncology in **2021** accounted for **21.7% of the total clinical trials** conducted. Active and new research accounts for **35.7%**, and clinical trials recruiting in subjects account for **10.4%**. Condition study found that most specific studies involved testing drugs for **Carcinoma (72.6%)**, the most common type of cancer. Most of the research is carried out in the USA (**47.2%**), China (**10.1%**), and France (**9%**).

Source: ClinicalTrials.gov

Oncology

In the sphere of **age-related oncology**, a lot of different study vectors exist. One of the most researched at present moment is **early diagnostics**. As well as that, new types of treatment methods emerge, such as **encapsulated drugs, vaccines, gene therapies, nanoparticles, epigenetic therapies, target medicine**. Treating cancer is a huge scientific problem; that is why a lot of research capacity is devoted to cancer **prevention and prediction**. Cancer research promotes **individual therapy** approach, as a result a lot of research is performed in this direction.

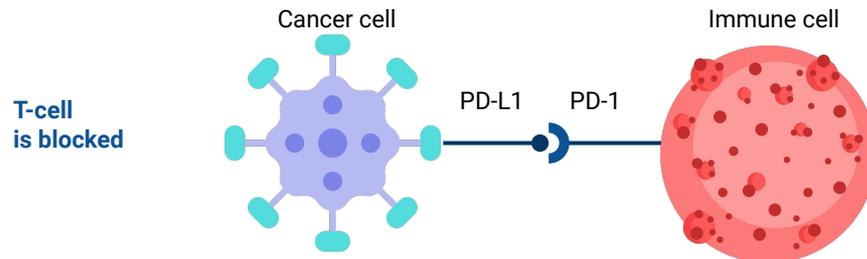
One of notable research fields is altering immune signaling for treatment. Such approach is represented by Nivolumab. **PD-1** - is a surface protein of T and B cells which is responsible for **downregulation of immune response** when activated. Some tumors develop surface protein PD-L1 - ligand to PD-L. **It can significantly decrease immune response to some tumors**. Nivolumab inhibits that regulation thus increases immune response to tumor. A phase 1 study is conducted by **National Cancer Institute (NCI)** to test the hypothesis that Nivolumab can be safely administered to patients.

Source: clinicaltrials.gov

Aging Analytics Agency

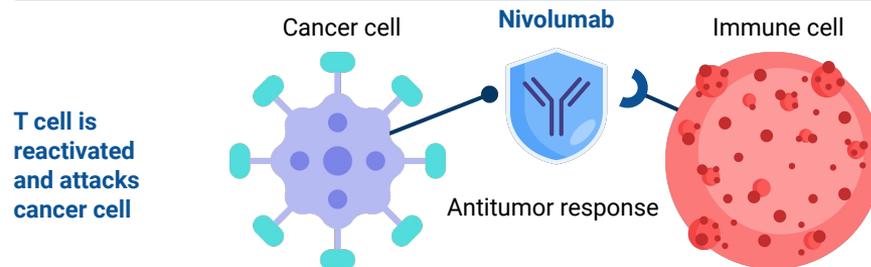
Anti-PD-1 Antibody Mechanism of Function

Without the antibody



When PD-L1 binds with PD-1, the cancer puts the brakes on immune cells (T cells) and blocks attacks on cancer cells.

With the antibody



Nivolumab removes the brakes on T cells by preventing PD-L1 from binding with PD-1, thereby reactivating T cells and allowing them to attack cancer cells.

CNS Conditions

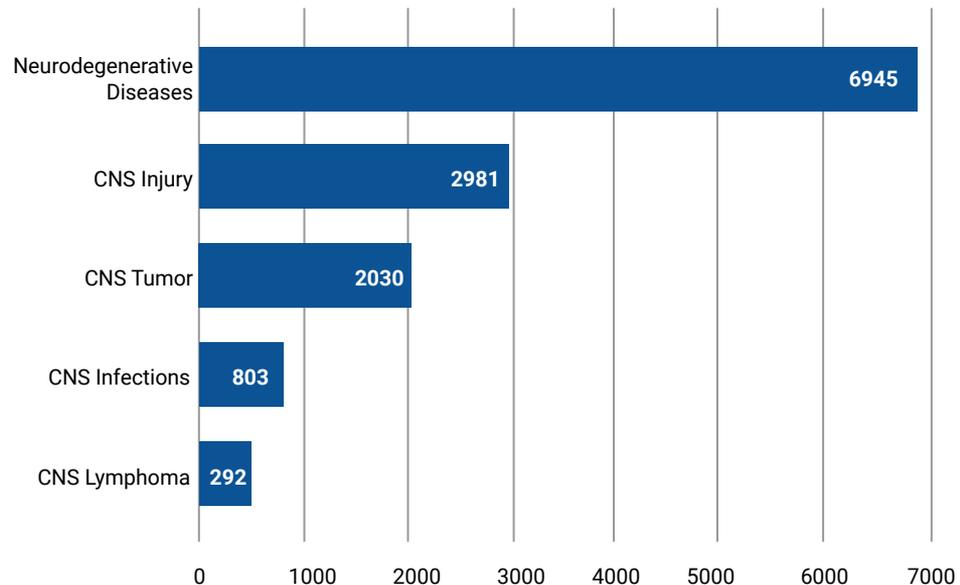
Central Nervous System (CNS) disorders are a group of neurological disorders that affect the structure or function of the brain or spinal cord.

The nervous system is vulnerable to various disorders, such as injuries, infections, tumors, etc. Thus, the clinical trials in CNS are mainly conducted in these areas.

The CNS Disorders are also closely related to cellular aging. Such neurological diseases as epilepsy, dementia or Parkinson's disease usually develop at an advanced age. The reason is the molecular mechanism of aging which involves genetic changes that cause the deterioration of the CNS. Clinical studies in this area aim to get a better understanding of aging in a section of Neurological diseases. Also much of research is focused on general nervous system disorders - such as peripheral nerve traumas. Therapy of such conditions greatly increase quality of life in old age.

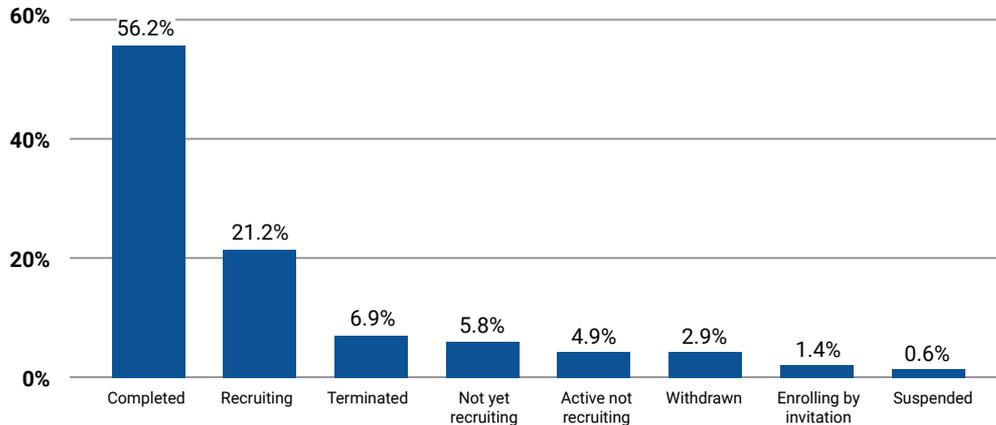
Source: ClinicalTrials.gov

The Main Types of CNS Studies by Total Number of Clinical Trials, Q1 2021

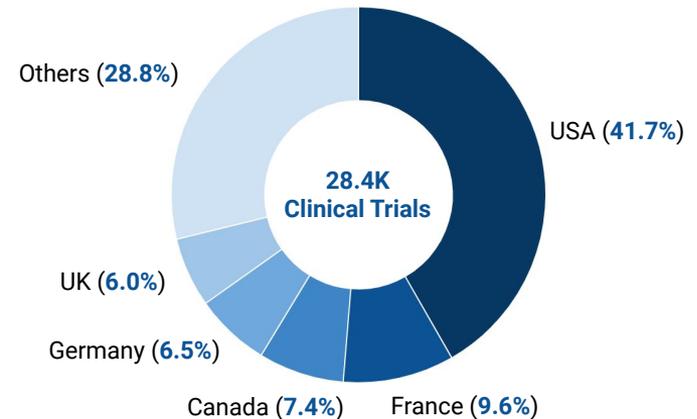


CNS Conditions

Status of Clinical Trials in CNS in Q1 2021



Top 5 Countries for Clinical Trials in CNS in Q1 2021



The number of clinical trials in CNS Diseases in **2021** accounted for **7.4% of the total clinical trials** conducted. Active and new research accounts for **43.8%**, and clinical trials recruiting in subjects account for **21.2%**. Most of the research is carried out in the USA (**41.7%**), France (**9.6%**), Canada (**7.4%**), Germany (**6.5%**) and UK (**6.0%**). The biggest part of clinical trials in CNS is in Not Applicable Phase (**29.8%**), which describes trials without FDA-defined phases, including trials of devices or behavioral interventions.

Source: ClinicalTrials.gov

CNS Conditions

Most of the researches are now focused at neurodegenerative diseases such as Alzheimer's syndrome or Parkinson's disease. Thus, just a fraction of, efforts is dedicated to less common diagnoses. As well as neurodegenerative diseases, schizophrenia is well studied due to its association with aging. Most of the companies are **developing multifunctional drugs that can share applications within several CNS conditions**, but their efficiency should be studied separately.

For example, **NKGen Biotech is developing autologous non-genetically modified natural killer cells** with enhanced cytotoxicity, which potentially can have a lot of applications for age-associated conditions. This therapy is being studied as a possible treatment for Mild Cognitive Impairment (MCI) and Alzheimer's Disease, as well as different types of cancer. Natural killer cells possess potential for eliminating any kind of deficient cell, thus field of clinical studied for this therapy will not be limited by cancer and CNS disorders.

More and more research arise in field of function restoration after trauma, thus it is a promising field for investigation.

Source: clinicaltrials.gov

Aging Analytics Agency

Most Relevant CNS Conditions Associated with Aging

Alzheimer's Disease and Other Memory Disorders

Ataxia

Huntington's Disease

Parkinson's Disease

Motor Neuron Disease

Multiple System Atrophy

Progressive Supranuclear Palsy

Metabolism Conditions

Metabolism conditions – disorders that relate to any intracellular and intercellular metabolism pathways.

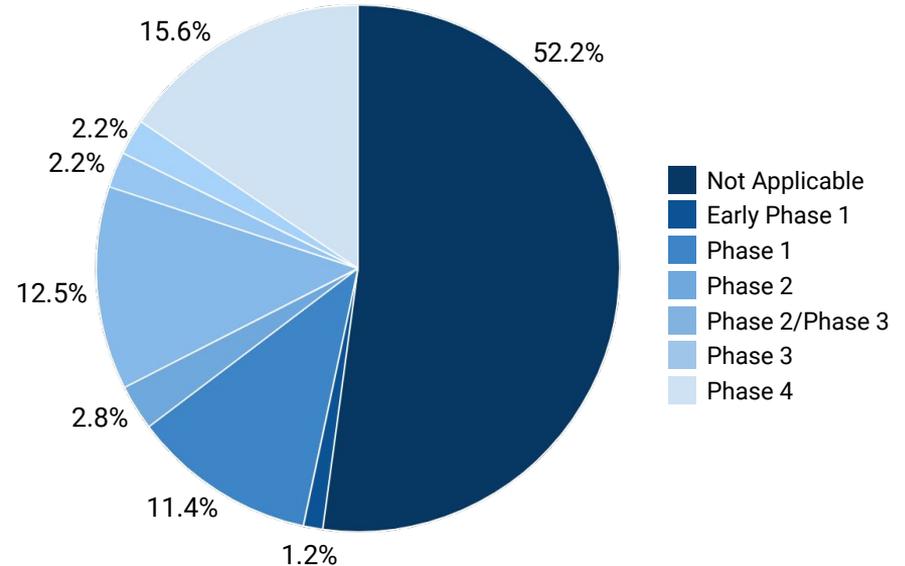
Diabetes is the most common metabolism disorder in population. It is a disease in which human blood glucose levels are too high. Its presence in population dramatically increases with age.

Key clinical trials and initiatives for diabetes include:

- 1 TrialNet** is an international network of researchers who are exploring ways to prevent, delay and reverse the progression of type 1 diabetes.
- 2 GRADE** is a comparative effectiveness study looking at what medications work best at lowering blood sugar levels in patients who are newly diagnosed with diabetes
- 3 RISE** includes 3 studies examining whether aggressive glucose lowering will lead to recovery of pancreas function in those with prediabetes and early type 2 diabetes.
- 4 D2d.** The goal of the Vitamin D and type 2 diabetes (D2d) study is to determine whether vitamin D supplementation is safe and effective for glucose metabolism in delaying the onset of type 2 diabetes.

Source: American Diabetes Association, The Lancet

Diabetes, Metabolic Disease, and Telomere Length

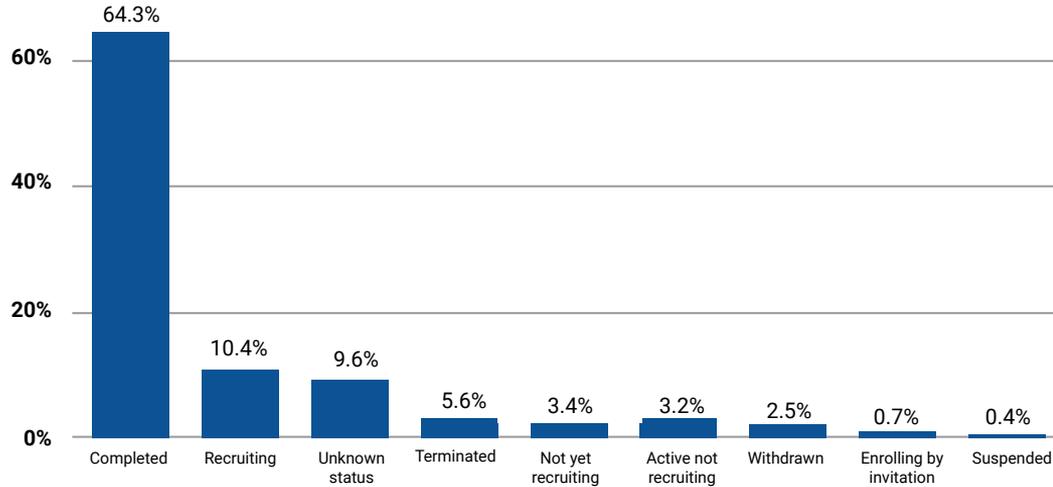


Note: Not Applicable - trials that are not regulated by FDA.

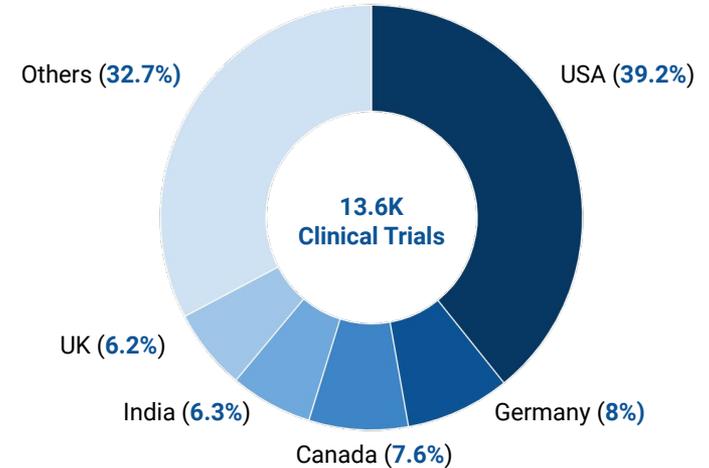
Phase 2/Phase 3 - trials that are in process of transition between Phase 2 and Phase 3.

Metabolism Conditions

Status of Clinical Trials on Diabetes in Q1 2021



Top-5 Countries for Clinical Trials on Diabetes in Q1 2021



The number of clinical trials of diabetes in **2021** accounted for only **3.6% of the total clinical trials** conducted. Active and new research accounts for **35.7%**, and clinical trials recruiting in subjects account for **10.4%**. Condition study found that most specific studies involved testing drugs for **Type 2 diabetes (72.6%)** because it occurs in 90% of people with diabetes. **27.4%** of clinical trials are associated with **Type 1 diabetes**, which occurs in only 10% of cases. Among all studies, the emphasis on the **Diabetes Mellitus study** is found in **48.8%** of clinical studies. Most of the research is carried out in the USA (**39.2%**).

Metabolism Conditions

Most modern metabolism related studies are connected with diabetes. Still, some researches are focused on intracellular metabolism alterations, which are commonly connected with metabolite deficiencies. Yet, the most promising trials are focused on intercellular metabolism and its modification, because such studies can have multiple applications.

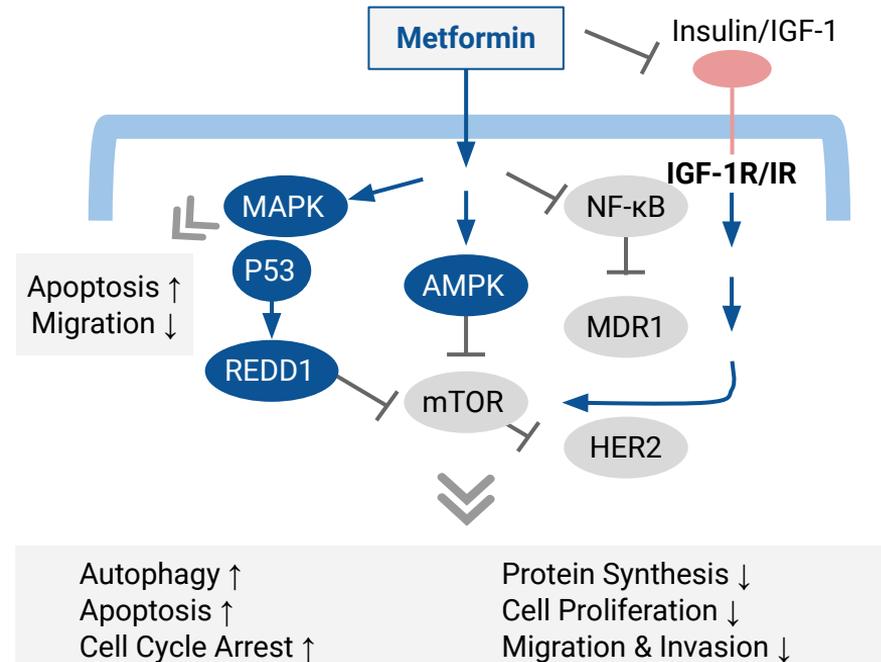
As example of such research: **Metformin** is classically referred to the first-line medication for the treatment of type 2 diabetes, but late clinical studies are expanding its therapeutic possibilities.

It is biguanide antihyperglycemic agent. It decreases glucose production by the liver, increasing the insulin sensitivity of body tissues and GDF15 secretion, thus improving general glucose metabolism.

During preclinical studies the **National Institute on Aging has discovered that the lifespan of the mice that were given small amounts of Metformin in their diet increased by 5.83%, at the same time**, the onset of age-related diseases began later for these mice. Due to fast development of metformin research a lot of different problems arise. Some studies show that use of metformin in elderly can promote inflammatory response, also evidence exists that use of this drug correlates with chronic kidney disease severity.

Source: Afar.org

Mechanism of Metformin Action



Note: Metformin has multiple target signaling cascades, they mostly influence metabolism of glucose. Glucose metabolism is one of key bases of cell function and viability.

Pain Management

Pain management is the process of providing medical care that alleviates or reduces pain. Mild to moderate pain can be treated with analgesic medications. For chronic pain, opiates and other narcotics may be used, sometimes in concert with analgesics; with steroids or nonsteroidal anti-inflammatory drugs when the pain is related to inflammation. New kind of physical therapeutics emerge on market, such as electro-pulse therapies. Psychological and psychiatric therapies are also a common option. Due to wide variety of pain etiology there is no universal key to solving that state and researches in that field would yet proceed for a long period of time.

The main division of clinical trials in pain management falls into different main categories such as diagnostics: **Pain analysis (56.4%** of clinical trials) and **Analgesia analysis (11.8%)**. Researchers focus is not only dedicated to pain measurement but to management strategies as well, such as developing new kind of safe medications.

Source: MedicineNet, Europe PMC

Key Pain Management Strategies

Oral Contraceptives

Physical Therapies (Electro-pulse, Massage, Ultrasound and Exercises)

Psychological Therapies (Cognitive Behavioural, Relaxation, Meditation)

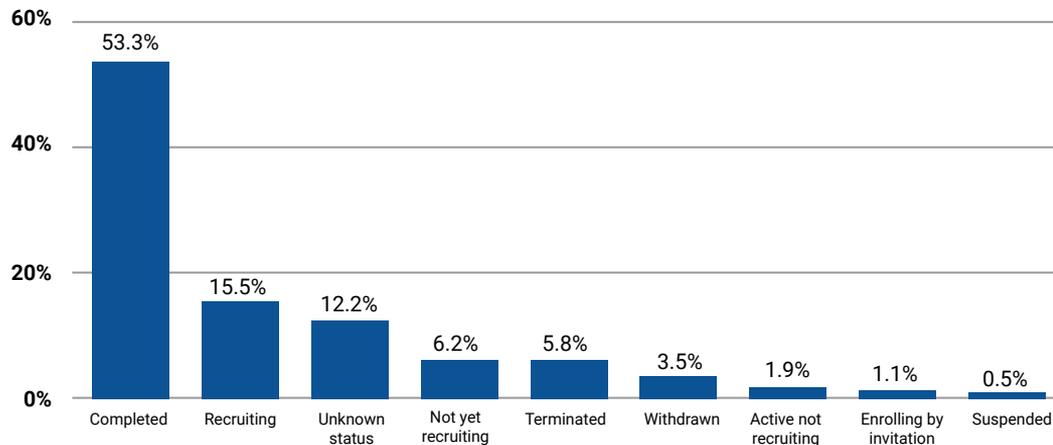
Diet Planning

Pain Mediators Inhibition

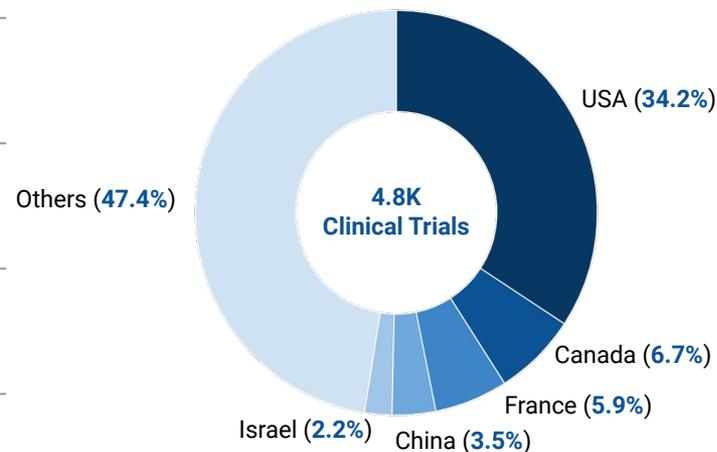
Pain Mediator Receptors Blocking

Pain Management

Status of Clinical Trials on Pain Management in Q1 2021



Top-5 Countries for Clinical Trials on Pain Management in Q1 2021



The number of clinical trials of pain management in **2021** accounted for only **1.2%** trials recruiting in subjects account for **15.5%**. Condition study found that most specific studies involved testing main groups: **drugs (56.6%)**, **procedures (20%)**, **of the total clinical trials** conducted. Active and new research accounts for **46.7%**, and clinical **devices (10.9%)** and **behavioral medicine approaches (6.4%)**. Most of the research is carried out in the **USA (39.2%)**, Canada (**6.7%**), China (**3.5%**), and Israel (**2.2%**).

Pain Management

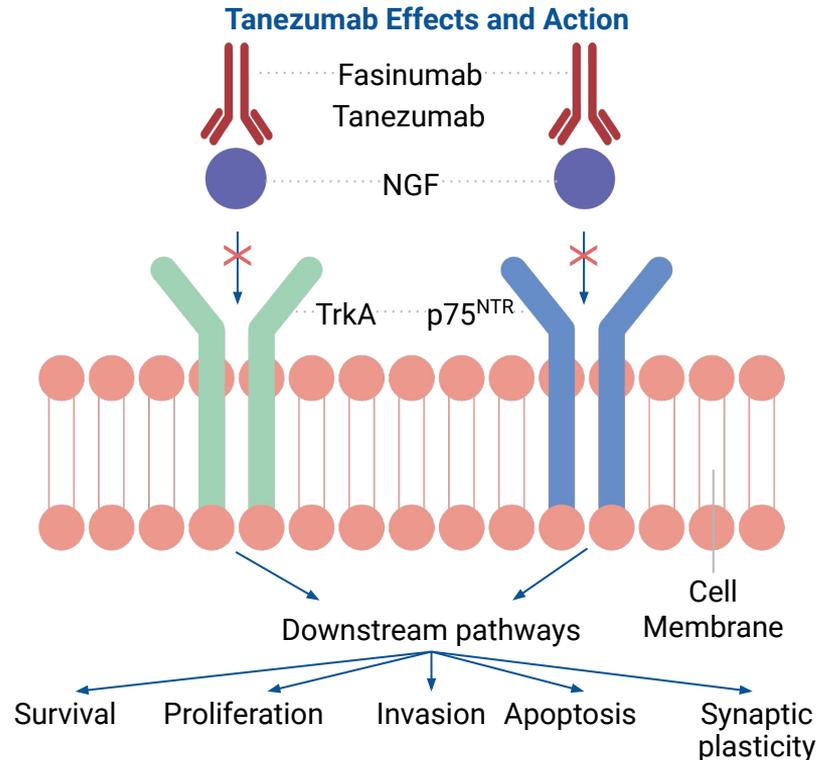
Pain management studies have always been focused on chronic pain cases, which is a majority of pain disorders. Still, some researchers develop field of analgesia. Tendency in pain management separate into alternative approaches: medication, physical therapy, psychological therapy. As well as in other fields, most valuable trials are of multi-applicable drugs.

Chronic low back pain comprises a major risk factor for the aging population. Recent study by **Pfizer** and **Eli Lilly and Company** reported promising results from phase 3 Study of Tanezumab in chronic low back pain. **Tanezumab** (codenamed RN624) is a monoclonal antibody against nerve growth factor (NGF). Linking of this antibody with NGF leads to inhibition of NGF pathway in neurons. Downregulation of this pathway is lowering cell activity thus decrease pain.

This study demonstrates the potential of **Tanezumab** to treat individuals suffering from moderate-to-severe chronic low back pain who have been unable to achieve relief with currently available medicines.

Source: Pfizer, ClinicalTrials.Gov

Aging Analytics Agency



Abbreviations: NGF: Nerve growth factor; TrkA: tropomyosin receptor kinase A; p75^{NTR}: p75 neurotrophin receptor.

Autoimmune Reactions

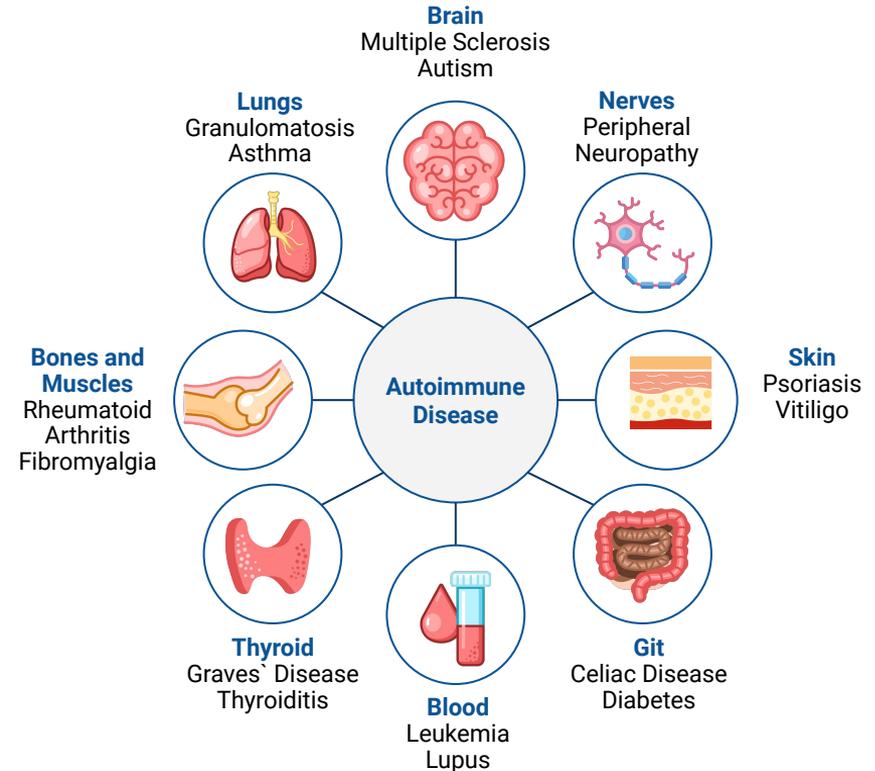
An autoimmune disease is a disorder when a person's immune system mistakenly attacks their own body. Inflammation could be a typical sign of such disorder.

The autoimmune diseases are among the **10 leading causes of death for women** and the number two cause of chronic illness in USA as well as a predisposing factor for cardiovascular diseases and cancer. Patients with some of autoimmune diseases have shown **a shorter life span** and are a model of accelerated immunosenescence. The main drawback of this group of diseases is chronic inflammation which continuously puts stress on all of components of organism.

The clinical trials in Autoimmune reactions are typically related to some specific diseases, such as Autoimmunity in the Pathogenesis of Atrial Fibrillation or Chronic Inflammatory Rheumatic Diseases. However, there are also more general studies, like the **Biomarkers in Autoimmune and Inflammatory Diseases** by Mayo Clinic, whose purpose is to identify biomarkers in people with autoimmune or inflammatory disease and in healthy people.

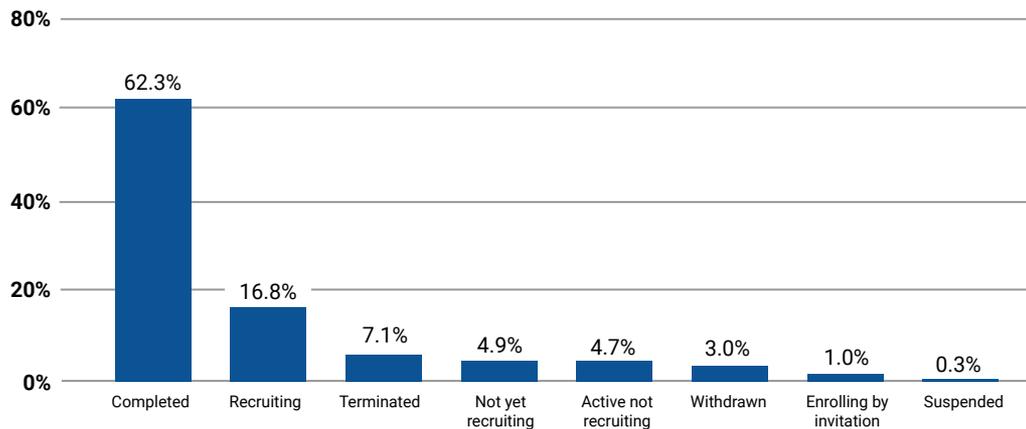
Source: Mayo Clinic

Variety of Autoimmune Conditions

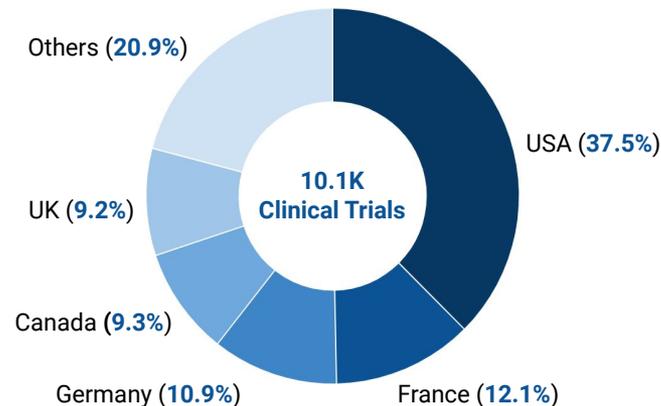


Autoimmune Reactions

Status of Clinical Trials on Autoimmune Reactions in Q1 2021



Top-5 Countries for Clinical Trials in Autoimmune in Q1 2021



The number of clinical trials concerning autoimmune reactions in **2021** accounted for **2.6% of the total clinical trials** conducted. Active and new research accounts for **37.7%** and clinical trials recruiting in subjects account for **16.8%**. Most of the research is carried out in the USA (**37.5%**), France (**12.1%**), Germany (**10.9%**), Canada (**9.3%**) and UK (**9.2%**). The vast majority of clinical trials concerning Autoimmune reactions is in Not Applicable Phase (**29.8%**), which describes trials without FDA-defined phases, including trials of devices or behavioral interventions.

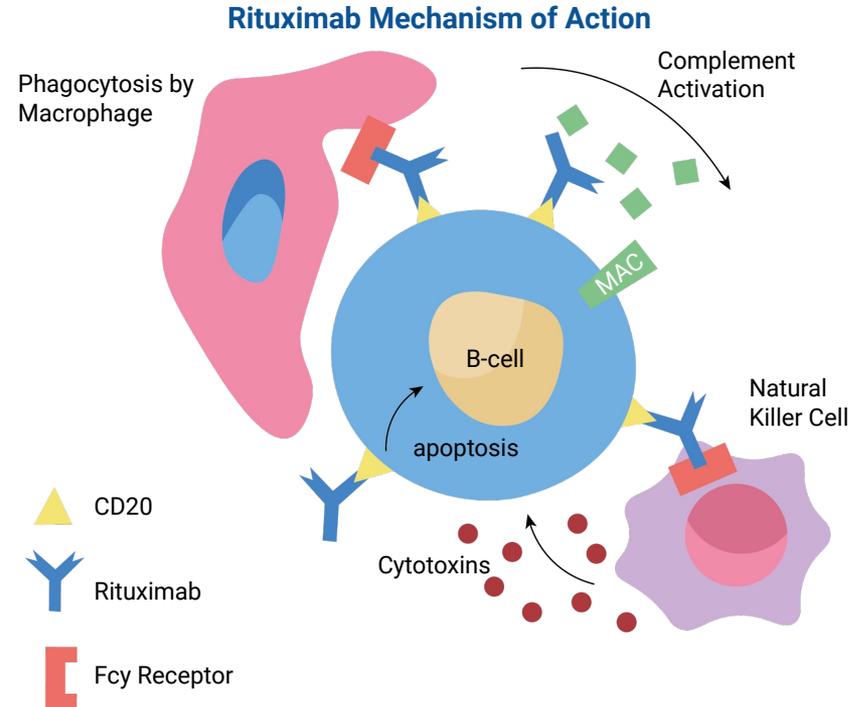
Source: ClinicalTrials.gov

Autoimmune Reactions

Autoimmune reactions are one of the most common age-related diseases, thus their research is a priority. Mostly research is focused on suppressing immunity but lately alternative ways of fighting such disorders emerged. Such as Immunity relaxation or targeted destruction of B-cells. Autoimmune disorders are mostly characterized by intensified activity of immune cells, thus the best approach to therapy is decreasing activity to normal level.

That approach was adopted by the group of researchers developing Rituximab. **Rituximab is a chimeric monoclonal antibody against the protein CD20**, which is primarily found on the surface of immune system B cells. B cells are responsible for multiple immune reactions, and their inactivation may lead to significant decrease of reaction. After binding with CD20 Rituximab triggers different cell cascades which lead to cell death. This drug has been involved in different clinical studies for almost 20 years now. It is progressively approved for treatment of different autoimmune diseases.

Source: [ClinicalTrials.Gov](https://clinicaltrials.gov)



Note: Rituximab mostly affect intercellular connections, thus leading to change in immune cell behavior.

Longevity Clinical Trials



Longevity Clinical Trials

Treatment of any disease starts with its diagnostics, that general rule perfectly applies to aging.

For a long time topic of precise determination of biological age was heavily argued, but lately new unified approaches were accepted by community. Mostly, **modern diagnostics of aging is based on detection and evaluation of biomarkers in different samples.** In case of existence of sample reference taken earlier in life, it is possible to determine biological age with accuracy.

Longevity clinical trials are focused on finding unified solution to fight aging, such solution in theory should expand life expectancy and provide better quality of life in elderly people.

Due to that, most promising vectors of research are; stem cell therapies and senolytics. Some of the approaches have already shown significant results, but yet only in animal models.

Source: clinicaltrials.gov

Blood-based Biomarkers for Geroscience-guided Trials

| Biomarker | Underlying Biologic Process & Role |
|----------------------------|--|
| IL-6, CRP TNFR1I | Inflammation & Intercellular Signaling Interleukin 6 (IL-6) is a proinflammatory cytokine and Tumor Necrosis Factor- α RII is a TNF α receptor involved in acute-phase response. C-Reactive Protein (CRP) is an acute phase protein produced in response to inflammation. Cytokine dysregulation is driver of pathophysiologic processes leading to disease, functional decline, frailty, and death. |
| GDF15 | Stress Response & Mitochondria Growth Differentiation Factor 15 (GDF15) is a member of the TGF- β superfamily robustly associated with mortality, cardiovascular events, cognitive decline and dementia. GDF15 is increasingly recognized in mitochondrial dysfunction, and as a biomarker of aging. |
| IGF-1 Insulin | Nutrient Signaling Disruption of the insulin/ insulin-like growth factor (IGF-1) signaling pathway is implicated in longevity in animal models. In humans, IGF-1 and fasting insulin are responsive to caloric restriction, and low IGF-1 in growth hormone receptor deficiency conveys disease protection. |
| Cystatin-C | Kidney Aging Cystatin-C, an extracellular inhibitor of cysteine proteases, is a marker of renal disease and aging. It is an independent risk factor for all cause and CVD-related mortality, and multi- morbidity, and higher levels are consistently associated with poor physical function and cognition. |
| NT-proBNP | Cardiovascular Health B-type natriuretic peptides (BNP, NT-proBNP) are secreted in response to cardiomyocyte stretching to decrease vascular resistance. NT-proBNP has a greater-half life and accuracy compared with BNP and is used to diagnose and establish prognosis for heart failure. |
| HGBA1c | Metabolic Aging Glycated hemoglobin (hemoglobin A1c. HGBA1c) is formed in a non-enzymatic glycation pathway and is a marker for 3-mo average plasma glucose. High HGBA1c reflects poor glucose control, and in older nondiabetics is strongly associated with death, chronic disease, and functional decline. |
| Molecular Signature | Epigenetic, Interdependent, Multi-Omic Data intensive molecular platforms can explore global changes in epigenetic, transcriptomic, proteomic, and proteostasis, and small metabolite signatures. These approaches may better capture complex and multifactorial processes underlying aging. |

Diagnostics and Measurement

Diagnostics refers to the process of determining what kind of disease or condition is causing patient's symptoms. Various kinds of tests and procedures are completed in order to diagnose aging, such as, but not limited to, hematogram, electrocardiogram (ECG), functional index, biomarkers identification.

All clinical trials share core requirements such as the need to exclude bias and provide evidence of effectiveness. However, **diagnostics trials differ from drug trials in many important ways.** As a result, diagnostics development requires substantial differences in planning, trial design and trial execution. For diagnostics developers, many development decisions depend on identifying the intended use and user, which in turn dictates a regulatory approval pathway, taking into account test complexity and role in patient-care decisions.

Source: MedicineNet

Comparison of Diagnostics and Prognostics

Diagnostics



Diagnostic and Continuous Monitoring Equipment



Biomarkers of Aging

- Complex multi-systemic biomarkers
- High cost to monitor
- New technologies need to be developed

Prognostics



Bioinformatics

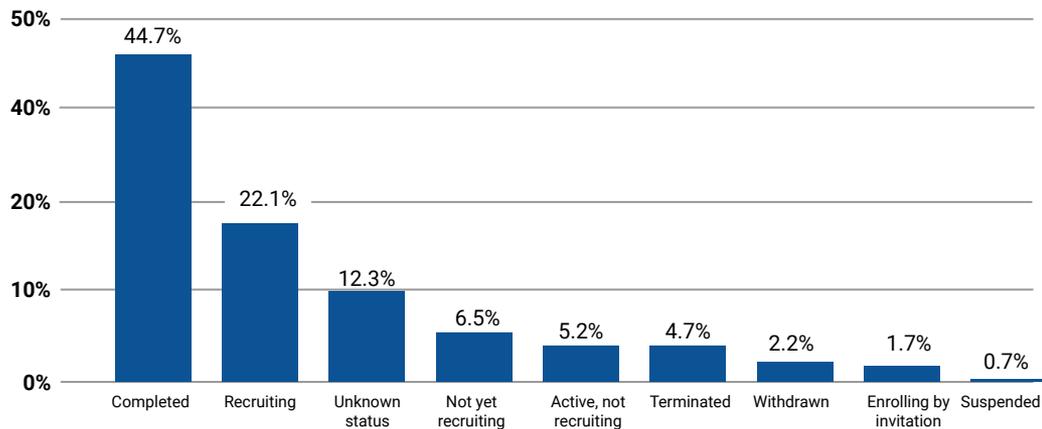


Next Generation Sequencing

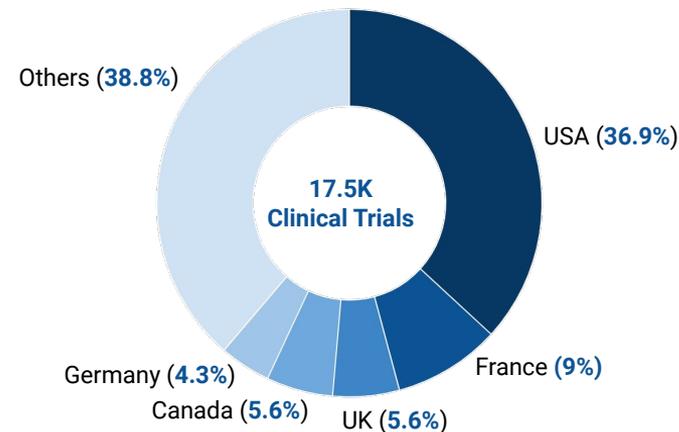
- Expert computer scientists needed
- Hardware and software requirements
- Big data quality and national integration

Diagnostics and Measurement

Status of Clinical Trials on Diagnostics and Measurement in Q1 2021



Top-5 Countries for Clinical Trials on Diagnostics in Q1 2021



The number of clinical trials of diagnostics and measurement in **2021** accounted for only **4.4% of the total clinical trials** conducted. Active and new research accounts for **35.4%**, and clinical trials recruiting in subjects account for **22.1%**. **4.4%** of clinical trials are in Phase 3, aimed at being the definitive assessment of how effective the diagnostic or measurement is, in comparison with the current 'gold standard' practices. Most of the research is carried out in the USA (**36.9%**) and France (**9%**).

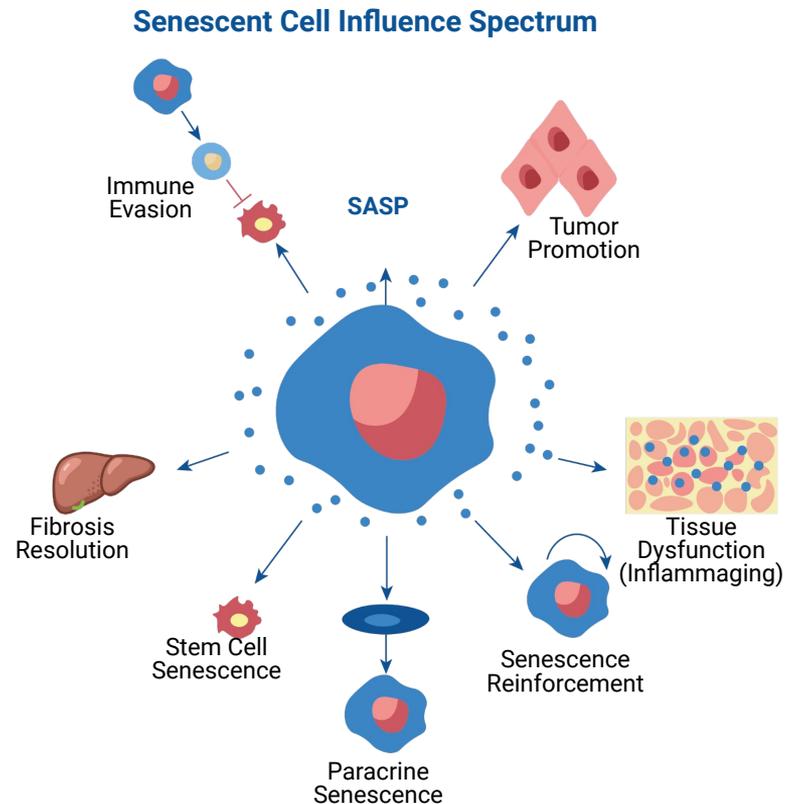
Cell Senescence

Cellular senescence is a key biological process underlying aging. It is described as **irreversible cell cycle arrest**, which leads to cell function decline or loss. Damaged senescent cells stay viable and metabolically active, they accumulate with aging and evidence suggests that their build-up promote numerous **age related pathologies**.

Lately, a group of preclinical studies have shown that elimination of senescent cells can significantly increase **quality of life and lifespan**. That led to focus of research community on development of ways for targeted elimination of senescent cells.

Due to those discoveries new class of therapeutics emerged - **senolytics and Senomorphics**.

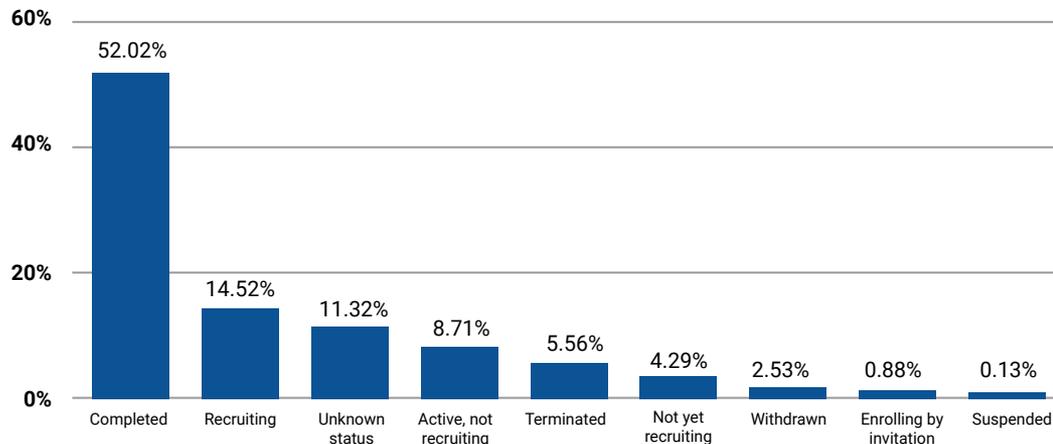
Senolytics are kind of compounds which selectively induce apoptosis in senescent cells. In turn **senomorphics** are drugs that are meant to decrease the impact of senescence cells on organism.



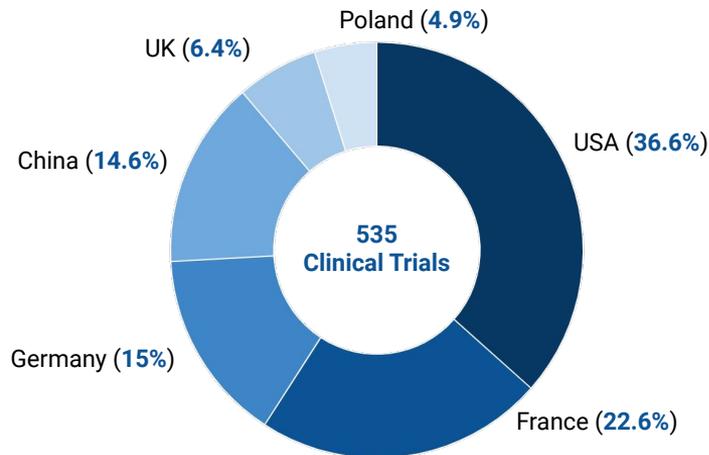
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Cell Senescence

Status of Clinical Trials on Cell Senescence in Q1 2021



Top-5 Countries for Clinical Trials on Cell Senescence in Q1 2021



As of Q1 2021, the percentage of clinical trials related to cell senescence is **negligible compared to the rest of hallmarks of aging**, Active and new research accounts for **30.4%** of the clinical trials, and clinical trials recruiting in subjects account for **15.4%**. **23.8%** of clinical trials are in Phase 3, aimed at being the definitive assessment of how effective the drug or intervention is, in comparison with the current 'gold standard' practices. Most of the research is carried out in USA (**36.6%**), France (**22.6%**), and Germany (**15%**).

Source: ClinicalTrials.gov

Genome Instability

Genetic instability refers to a **range of genetic alterations from point mutations to chromosome rearrangements**. This, in turn, is associated with premature aging, inherited diseases and various types of cancer.

According to the **NIH U.S. National Library of Medicine** currently (on the 1st of July, 2021) there are **669** active clinical trials on the Genomic Disorder topic.

One of the most perspective technologies in modern Genetic Engineering is **CRISPR**, which is a powerful tool for editing genomes. More specifically, **CRISPR-Cas9** is an **efficient** and relatively cheap technology, which has gained popularity in recent year, because it can cleave nearly any sequence complementary to the guide RNA.

Source: ClinicalTrials.gov

Causes of Genome Alterations

Replication Dysfunction

Postreplicative Repairs Failure

Failures in Recombination

Site-specific Hotspots of Instability

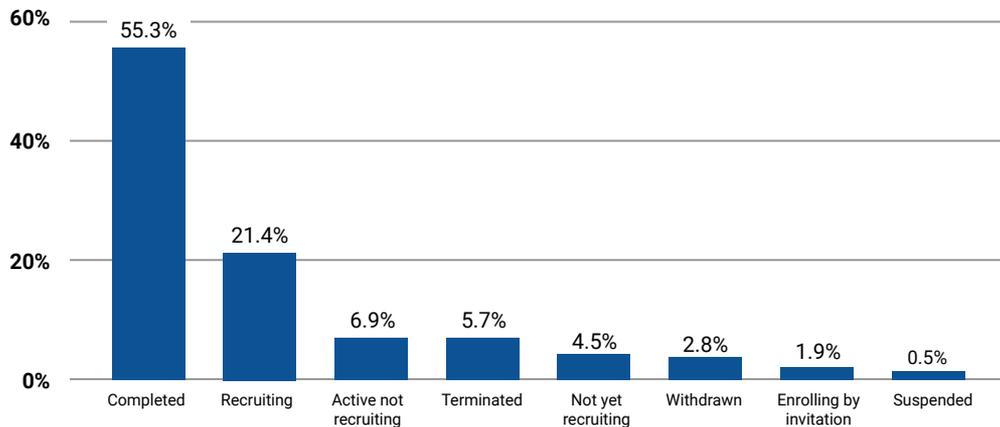
Chromosome Breakage

Microsatellite Rearrangement

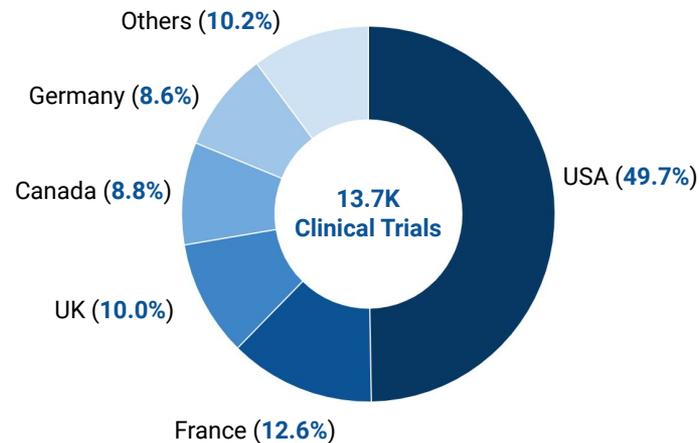
Substitutions, Deletions, Insertions of Nucleotide

Genome Instability

Status of Clinical Trials on Genetics in Q1 2021



Top-5 Countries for Clinical Trials on Genetics in Q1 2021



The number of trials associated with genome instability is taking one **of major segments of clinical trials** sector. Most of the research is carried out in the USA (**49.7%**), France (**12.6%**), UK (**10.0%**), Canada (**8.8%**) and Germany (**8.6%**). The majority of clinical studies related to genomic instability are at the completed stage (**55.3%**), although active and recruiting trials are also numerous (**21.4%**). This implies that the field of this study is dynamic and develops rapidly. Small number (**2.8%**) of withdrawn trials show that field of this research has high success rates, which might be helpful for investment.

Source: ClinicalTrials.gov

Mitochondrial Dysfunction

Mitochondria are the powerhouses of the cells in bodies.

Present in every cell in body, their malfunction results in a cascade of health conditions. Everyone faces a noticeable reduction in ATP generation and increased electron leakage in the respiratory chain caused by aging. Such decrease in function is called Mitochondrial Dysfunction.

According to the NIH U.S. National Library of Medicine, currently (on the 1st of July, 2021) there are **77** active clinical trials on the Mitochondrial Dysfunction topic, 28 of them are completed, 29 - active.

Mitochondrial dysfunction is considered one of the hallmarks of aging, yet **combating it has proven to be difficult**, which explains a relatively small number of trials. These challenges stem from the ubiquitous nature of mitochondria, genetic complexity with dual genome control, the presence of heteroplasmy associated with most variants in mtDNA, and the heterogeneous clinical presentations associated with multi-organ involvement in various mitochondrial disorders.

Source: MedicineNet, Europe PMC

Prominent Mitochondrial Dysfunction Clinical Trials

Mitochondrial dysfunction in Neurodegenerative disorders

Mitochondrial Dysfunction in Cancer

Role Mitochondria in Metabolic disorders

Antioxidant Therapy Effect on Mitochondrial Dysfunction

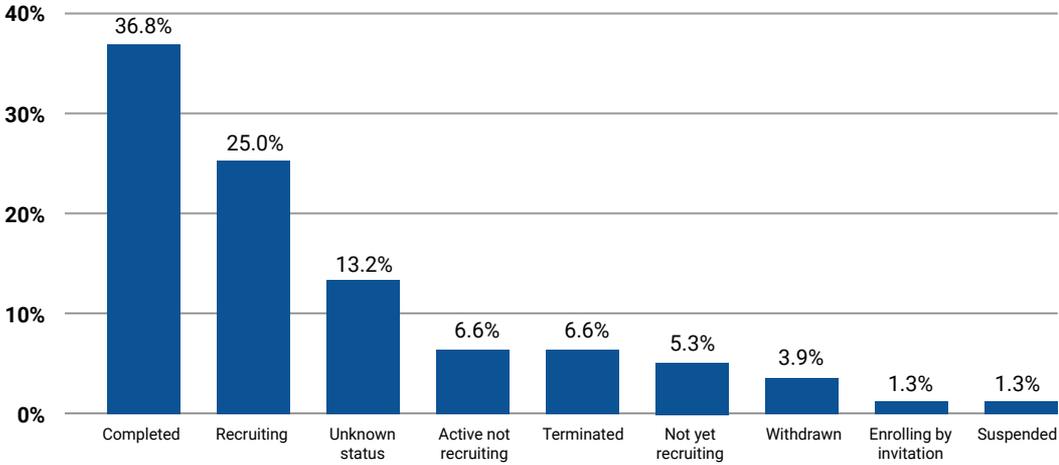
Mitochondria in Wound Healing

Mitochondrial and Chronic Kidney Disease

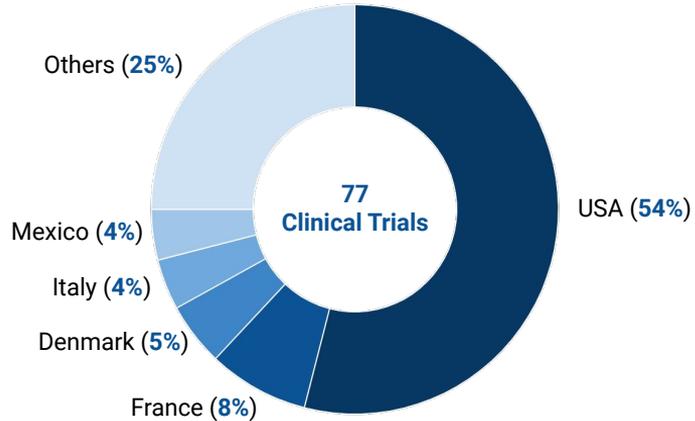
NAD+ Therapy Effect on Mitochondrial Dysfunction

Mitochondrial Dysfunction

Status of Clinical Trials on Mitochondrial Dysfunction in Q1 2021



Top-5 Countries for Clinical Trials on Mitochondrial Dysfunction in Q1 2021



As of 2021, the percentage of clinical trials related to mitochondrial dysfunction is **negligible compared to the rest of hallmarks of aging**, yet 13% those that passed up to phase 3 and 4, meaning that the industry-ready products are feasible in the nearest future. Most of the research is carried out in the USA (54%), France (8%), and Denmark (5%).

Source: ClinicalTrials.gov

Stem Cell Reserve Exhaustion

Stem cell reserve exhaustion is a state which is characterized by age-related deficiency of stem cells. **Stem cell potential** maintains immunity and regenerative potentials and its deficit results in malfunction of those systems.

Stem cell reserve exhaustion is believed to be one of **key reasons of aging**. Due to that research is heavily focused on conquering this phenomena by different approaches. Despite the fact that some stem cell therapies were controversial for a long period of time, the field is continuously **emerging new methodologies**.

At present moment more potential therapies are in state of clinical trials than being used. Most of them are focused on preservation and restoration of present cells and quantity magnification or introduction of new cells.

It is generally accepted that this vector of research is the most promising of all approaches to the fight against aging.

Stem Cell Reserve Therapies

Stem Cell Transplantation

Stem Cell Preservation

Inducing Pluripotent Stem Cells

Stem Cell Restoration

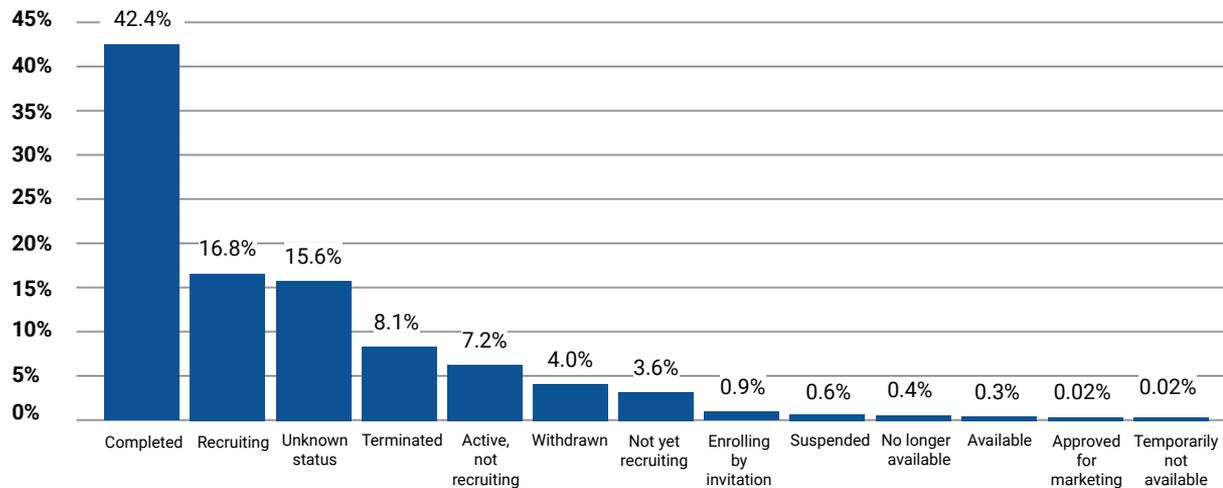
Reducing Stem Cell Inhibition

in vitro Quantity Magnification

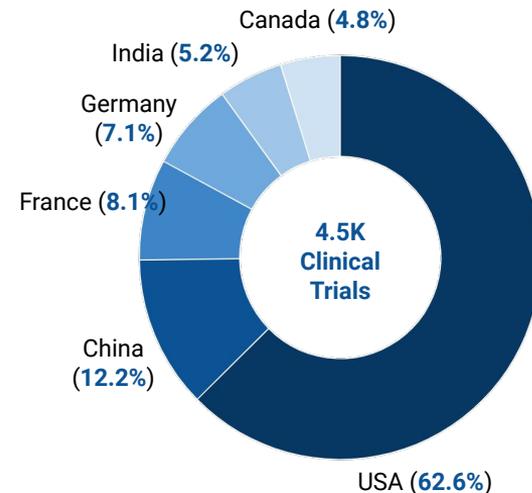
Note: Vast quantities of different therapies were grouped by approach.

Stem Cell Reserve Exhaustion

Status of Clinical Trials on Stem Cell in Q1 2021



Top-5 Countries for Clinical Trials on Stem Cells in Q1 2021



As of Q1 2021, the percentage of clinical trials related to stem cell reserve exhaustion is **1.2% of all clinical trials**. Active and new research accounts for **28.5%** of the clinical trials, and clinical trials recruiting in subjects account for **17.7%**. **9.7%** of clinical trials are in Phase 3, aimed at being the definitive assessment of how effective the drug or intervention is, in comparison with the current 'gold standard' practices. Most of the research is carried out in USA (**62.6%**), China (**12.2%**), and France (**8.1%**).

Source: ClinicalTrials.gov

General Inflammatory Background

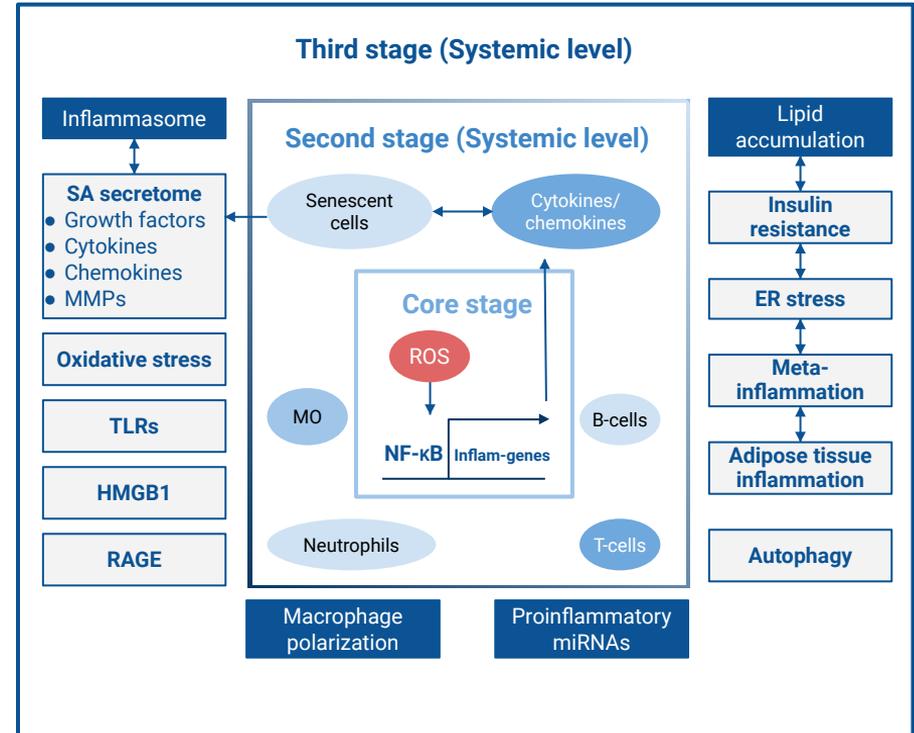
Inflammation is a defence mechanism of living organisms that is aimed at increasing chances of survival. Short-term, acute inflammation is a first-line defense mechanism that acts against harmful agents, such as pathogens, toxins, or allergens.

Under normal conditions, the tightly coordinated actions of various defense components including immune cells, endogenous anti-inflammatory agents, and tissue remodeling processes enable the resolution of acute inflammation. However, when this intricate acute inflammatory response fails to resolve and persists, more defense components are mobilized to create a long-term unresolved immune response known as **chronic inflammation**.

While not being recognized among hallmarks of aging, chronic inflammation is linked to **altered cell communication** and **epigenetic alterations**. It is involved in onset of type 2 diabetes, atherosclerosis, and obesity, conditions that contribute and contribute to aging.

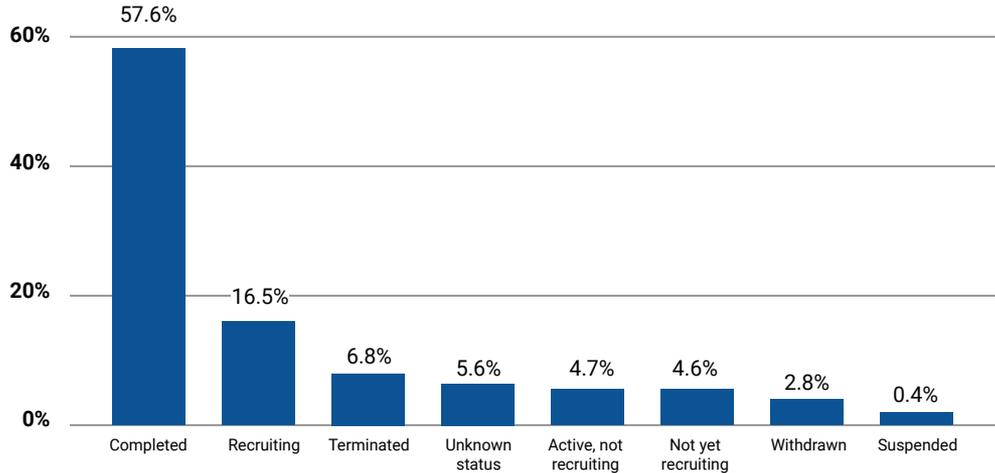
Source: Chung et al., 2019

Conceptual Framework of Age-related Inflammation

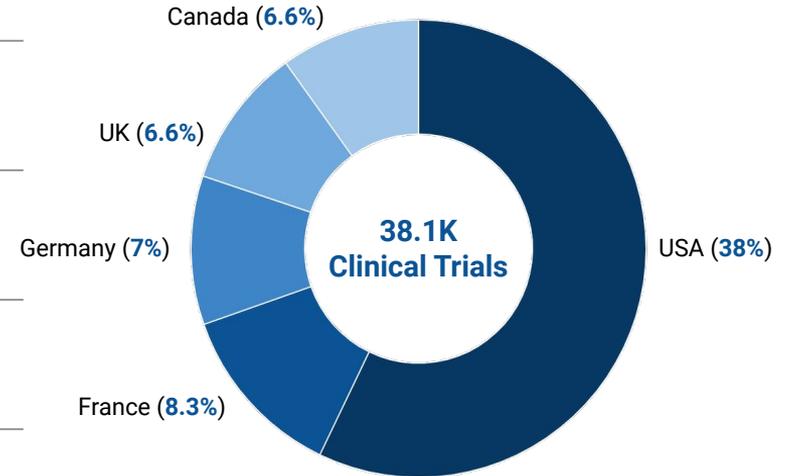


General Inflammatory Background

Status of Clinical Trials on GIB in Q1 2021



Top-5 Countries for Clinical Trials on GIB in Q1 2021



Clinical studies related to **General inflammatory background** account for **9.9%** in 2021 of all clinical trials. **96.9% of trials include people over 64 years old.** **46.5%** of trials were conducted for drug development, **10.8%** for devices, **9.5%** for procedures, and only **8.7%** were related to behavioral medicine approaches.

15.5% of the trials are associated with special clinical studies of the **biomarkers of human longevity**, and **0.6%** with the **inflammatory background analysis.**

Source: ClinicalTrials.gov

Altered Intercellular Communication

Altered intercellular communication is the change in signals between cells that can lead to disabilities of aging and disfunction, inflammaging, immunosenescence, bystander effects. One of the most prominent and important changes in intercellular signaling that occurs with age is an increase in continuous 'background' inflammatory signaling. The main direction of clinical and preclinical studies of changes in intercellular communication is the development of drugs and blood transfusion with an analysis of its effect on slowing aging in body tissues. These include clinical trials, divided into 2 groups:

1

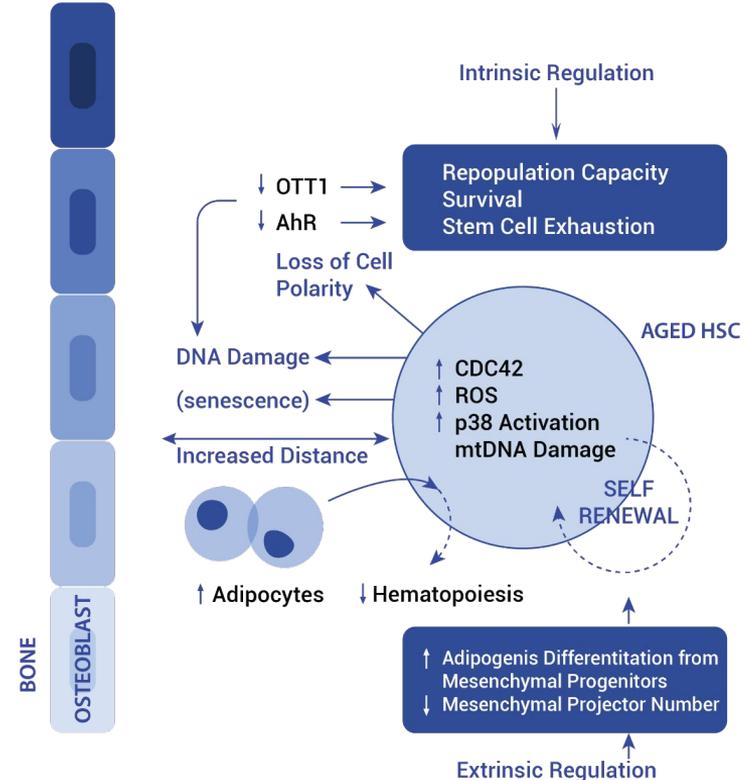
AKST-4290 and GRF602. These studies are related to the drugs **Eotaxin** (using a chemokine whose levels increase in blood plasma as we age) and GRF6021 (targeting altered intercellular communication in patients with Parkinson's Disease)

2

Studying whether the **RTB101 mTORC1 inhibitor** (small molecule licensed from Novartis) is capable of protecting older adults from developing COVID-19 after exposure.

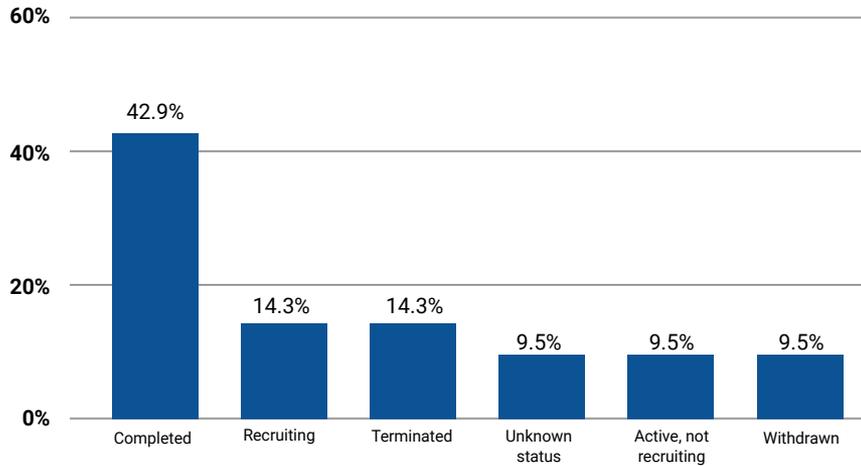
Sources: AgeCurve, Merck

Altered Intercellular Communication

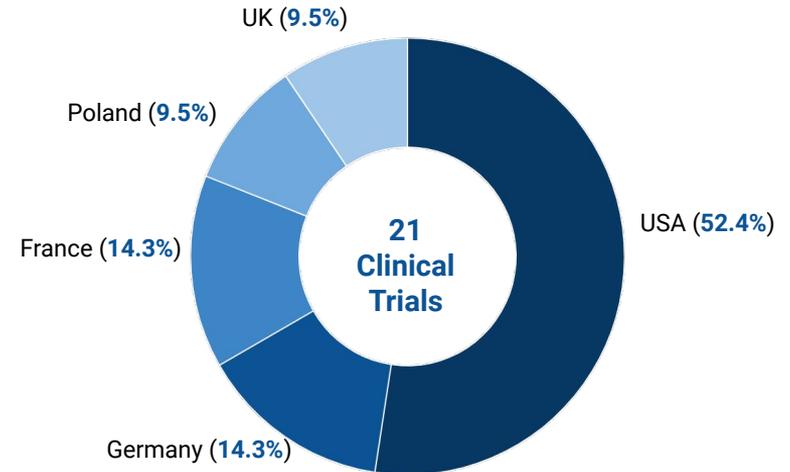


Altered Intercellular Communication

Status of Clinical Trials on AIC in Q1 2021



Top-5 Countries for Clinical Trials on AIC in Q1 2021



Clinical studies related to altered intercellular communication account for only **0.01%** in 2021 of all clinical trials. They were attended by 1997 people, of which **54.3% are over 65 years old**. **42.8%** of research was related to drug development, **14.3%** was related to procedures, and only **4.7%** was related to behavioral medicine approaches. In addition, 9.5% of clinical trials are conducted in parallel with COVID19 trials. **23.8% are associated with clinical studies of the first group (AKST-4290 and GRF6021), and 19.1% with the second group (RTB101)**, the rest were sent to other intercellular clinical trials.

Source: ClinicalTrials.gov

Cell Signaling and Autophagy

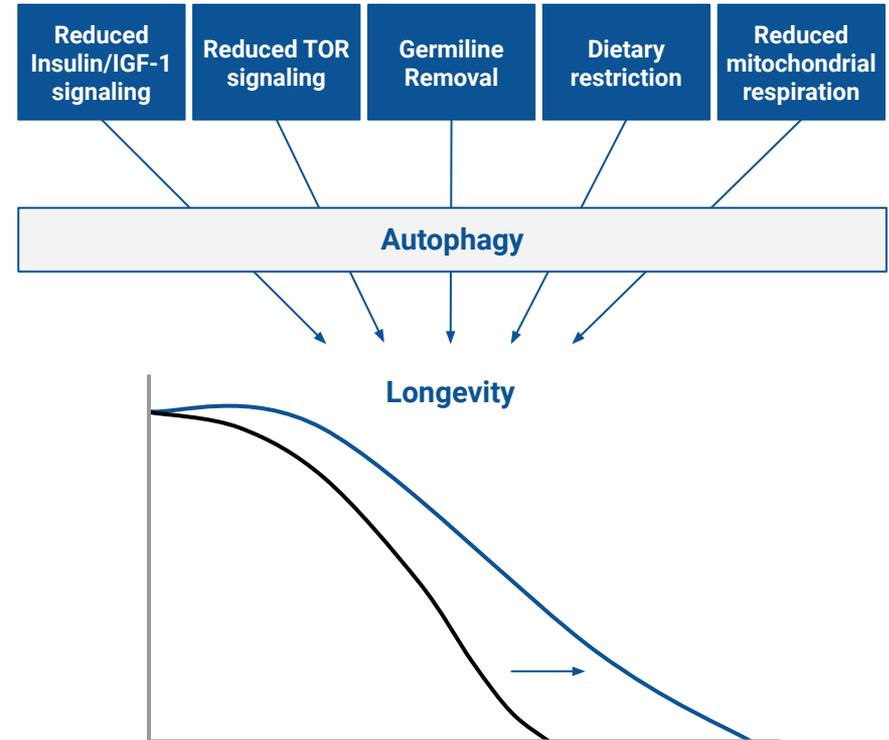
Aging is continuous loss of function, small alterations in signaling which is slowly changing with age contribute to it. But due to the enormous variety of possible dysfunctions, it is hard to outline major groups. Loss of autophagy potential is one of consequences of altering cell signaling.

Macroautophagy is a vacuolar, self-digesting mechanism responsible for the removal of long-lived proteins and damaged organelles by the lysosome. Recent genetic evidence indicates that autophagy has a crucial role in the regulation of lifespan in animals. Pharmacological treatments have been shown to extend lifespan through activation of autophagy, indicating that autophagy could be a potential and promising target for modulation of animal **lifespan**.

Clinical trials are ongoing to increase autophagy in order to fight such conditions as neurodegenerative diseases, cancer, Alzheimer's and Huntington's diseases.

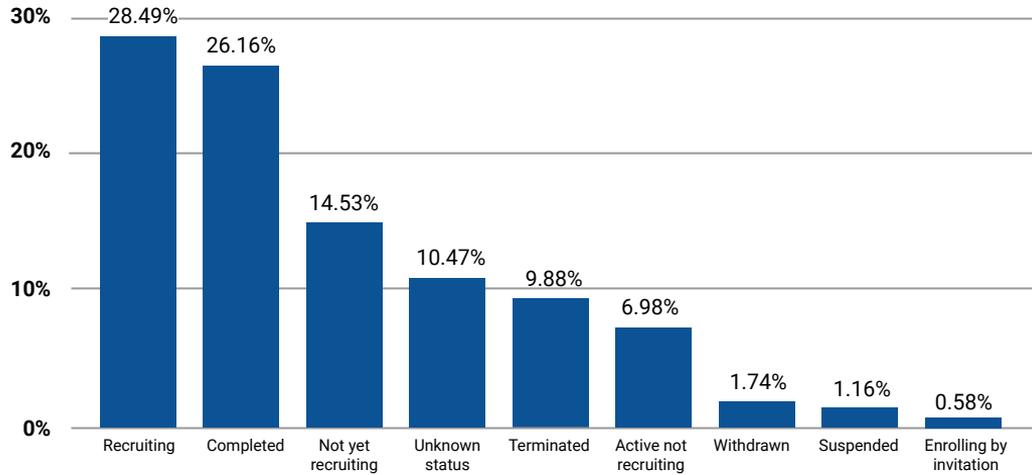
Source: ClinicalTrials.gov

Approaches that Contribute to Autophagy Increase

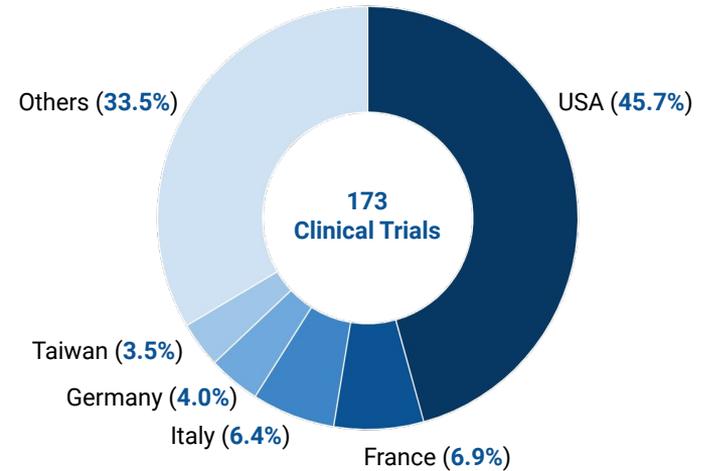


Cell Signaling and Autophagy

Status of Clinical Trials on Autophagy in Q1 2021



Top-5 Countries for Clinical Trials on Autophagy in Q1 2021



The number of clinical trials of autophagy in **2021** is 173. Condition study found that most specific studies involved testing main groups: **drugs (56.6%)**, **procedures (20%)**, **of the total clinical trials** conducted. Active and new research accounts for **46.7%**, and clinical **devices (10.9%)** and **behavioral medicine approaches (6.4%)**. Most of the research is carried out in the USA (**45.7%**), France (**6.9%**), Italy (**6.4%**), and Germany (**4.0%**).

Longevity Drugs in Phase I Clinical Trials

Clinical Phase I is focused on **dose-ranging on healthy volunteers** for safety analysis. Due to the aforementioned reasons, the number of drugs taking part in the clinical studies is significantly smaller. The distribution of the biological approaches stays close to the one seen in the Preclinical Phase.

| Company | Drug Candidate | Company | Drug Candidate |
|---|--|---|--|
|  salk Where cures begin. | J147 to treat the Alzheimer's disease and reverse some processes of aging |  | DNL747 reduces brain inflammation |
|  Amazentis | Urolithin A to prevent mitochondrial aging |  | DNL343 restores RNA and protein function |
|  | Evaluating therapeutic effects of the transplantation of MNV-BM-BLD |  | DNL151 to treat the Parkinson's disease |
|  BlueRock Therapeutics | CELL+GENE platform to create Parkinson's disease treatment |  | DTL201 and DTL151 to restore lysosomal function and treat the Parkinson's disease |

Longevity Drugs in Phase I Clinical Trials

| Company | Drug Candidate | Company | Drug Candidate |
|---|--|--|--|
|  Immunic THERAPEUTICS | Developing IMU-856 , a compound that targets a transcriptional regulator of immune barrier function |  Epirium | Evaluating Biomarker Response to (+)-Epicatechin in Becker Muscular Dystrophy |
|  BlueRock Therapeutics | Testing surgically injecting nerve cells that make dopamine |  NUS National University of Singapore | Alpha-ketoglutarate (AKG) - regenerative medicine focused on metabolism stabilisation |
|  CohBar INC. | CB4211 for Fatty Liver Disease treatment |  tomorrowlabs | Investigation of a Proprietary Cosmeceutical to Reduce the Visible Signs of Cutaneous Aging |
|  Alterity THERAPEUTICS | ATH434 to treat the Alzheimer's and Parkinson's disease |  Droclara BIOSCIENCES™ | General Amyloid Interaction Motif (GAIM) to disrupt amyloid aggregates |
|  CytoMed Therapeutics 新细胞医学 | MSC Infusion for anti-aging and regenerative therapy |  WISCONSIN UNIVERSITY OF WISCONSIN-MADISON | Inorganic Nitrate Supplementation on Cerebrovascular Aging and Arterial Stiffness Study |
|  The Sinclair Lab BLAVATNIK INSTITUTE GENETICS | Umbilical Cord Mesenchymal Stem Cells Infusion for Aging Frailty |  MAYO CLINIC | Use of Platelet Rich Plasma (PRP) for Facial and Hand Skin Rejuvenation |
|  聖釋 SCL now® | hUC Mesenchymal Stem Cells for treatment of Cirrhosis |  Intervene Immune | Human growth hormone (HGH) and dehydroepiandrosterone (DHEA) to regrow the thymus |

Longevity Drugs in Phase II Clinical Trials

Clinical Phase II is one of the most important stages in Clinical Trials, since it could propel the drug to Phase III, which is always considered the most complicated and expensive. Thomas J Hwang with his team assessed **640 phase 3 trials** with novel therapeutics and found that **54%** of them failed to further proceed from phase II. **57%** of those failures happened due to inadequate efficacy in humans.

| Company | Drug Candidate | Company | Drug Candidate |
|---|--|---|--|
|  | MIB-626 for metabolism normalisation |  | UBX1325 for removing senescent cells |
|  | The patient's own lymph nodes for organs replacement |  | Chronokines (plasma fractions) for rejuvenation |
|  | Allogenic mesenchymal stem cells (MSCs) for treating age-related diseases |  | Assess the Efficacy and Safety of AKST4290 |
|  | Mesenchymal stem cell (MSC) therapy to treat age-related frailty |  | Assess the Safety of GRF6021 Infusions |

Source: <https://www.sciencedirect.com/science/article/pii/S2451865418300693?via%3Dihub>

Longevity Drugs in Phase II Clinical Trials

| Company | Drug Candidate | Company | Drug Candidate |
|---|--|--|--|
|  THERAVASC | Sodium Nitrite to Treat Arterial Aging |  UT Health San Antonio | Nicotinamide Riboside in COVID-19 Patients for Renal Protection |
|  BIOAGE | Developing BGE-117 , that inhibits an enzyme responsible for breaking down Hypoxia-Inducible Factor |  UT Health San Antonio | Metformin for preventing frailty in high-risk older adults |
|  agelessRx | Evaluation of aging with Rapamycin for Longevity Study |  BIOAGE | Evaluating BGE-175 in hospitalized adults with COVID-19 |
|  LONGEVERON | Longeveron Mesenchymal Stem Cells to treat Aging Frailty |  CBMG Cellular Biomedicine Group | Mesenchymal Progenitor Cells for the treatment of Knee Osteoarthritis |
|  ChromaDex. | Nicotinamide riboside (NR) converting the different B3 vitamins into NAD+ |  FREQUENCY THERAPEUTICS | FX-322 in Adults With Stable Sensorineural Hearing Loss |
|  Scholar Rock | SRK-015 for spinal muscular atrophy (SMA) treatment |  Genome Protection | Entolimod on Immunosenescence in healthy geriatric subjects receiving Influenza vaccination |

Longevity Drugs in Phase II Clinical Trials

| Company | Drug Candidate | Company | Drug Candidate |
|--|--|---|--|
|  HUMACYTE [®] | Humacyte Human Acellular Vessel (HAV) in patients with vascular trauma |  MAYO CLINIC | Dasatinib + Quercetin for senescence in Chronic Kidney Disease |
|  Intervene Immune | Thymus Regeneration, Immuno restoration, and Insulin Mitigation Extension Trial (TRIIM-X) |  MAYO CLINIC | Nicotinamide Riboside + Pterostilbene for Protection From Acute Kidney Injury (AKI) |
|  LYGENESIS | Allogenic Hepatocyte transplantation into Periduodenal Lymph Nodes |  MAYO CLINIC | Fisetin to remove senescent cells |
|  LINEAGE CELL THERAPEUTICS | Evaluating of the safety and tolerability of OpRegen |  rejenevie THERAPEUTICS | Hematopoietic stem cells (HSCs) - regenerative treatment for restoring stem cell balance. |
|  biophytis LIVE LONGER, LIVE HEALTHIER | Sarconeos to treat sarcopenia and age-related loss of muscle mass |  Scripps Research | Quercetin and Dasatinib to destroy senescent cells |
|  RETROTOPE | RT001 in Amyotrophic Lateral Sclerosis |  Stealth BIOTHERAPEUTICS | Elamipretide in subjects with AMD With Non-central GA |

Longevity Drugs in Phase III Clinical Trials

After completion of early clinical phases I and II research gets significantly scaled by number of participants. **Phase III of clinical trials** is determined to define the effect of a drug or method on some condition in certain population, thus support eventual New drug application and potential approval. That is why for maximised precision of an output sample group is randomised. Number of participants often strongly depends on type of procedure being investigated and frequency of condition cases in population. The process of evaluation tends to last for 1-4 years and only 25% of drugs pass this milestone.

Biosplice Lorecivivint performed as a safe and well-tolerated drug during Phase II. Phase III of this trial is intended to support an eventual New Drug Application approval of lorecivivint as a potential drug to treat osteoarthritis.

SkQ1 (Mitotech) is a drug that demonstrates statistically significant superiority over placebo, is comfortable and well-tolerated and causes no severe or unexpected ocular adverse events. After entering Phase III drug initially shows positive results.



SkQ1: a
mitochondrial
antioxidant

Lorecivivint: for
restoring the Wnt
signaling pathway

Elamipretide in
subjects with
Barth Syndrome:
a mitochondrial
antioxidant



**Mitochondrial
Dysfunction**

**Altered
Intercellular
Communication**

**Mitochondrial
Dysfunction**

Longevity Drugs in Phase III Clinical Trials

Netarsudil is a first-in-class therapy for the treatment of patients with open-angle glaucoma, ocular surface diseases and retinal diseases. Prior to passing to Phase III clinical trials it has shown great results. It is active small metabolite, which is administered once a day in the evening, in form of eye drops. The mechanism of action of this medication is not completely known. The enzyme rho kinase is inhibited by it. This appears to enhance aqueous humor outflow via the trabecular meshwork while simultaneously lowering pressure in the episcleral layer's veins.

Pimavanserin is a drug that should reduce Neuropsychiatric Symptoms Related to Neurodegenerative Disease in Adult and Elderly Subjects. Pimavanserin acts as an inverse agonist and antagonist at 5-HT serotonin receptors, thus altering signaling. At present moment studies are focused on it's f Parkinson's disease treatment application.

RT001 is an experimental fatty-acid from **Retrotope** that stabilizes the mitochondrial and cellular membranes against attacks and restores cellular health. Researchers at Retrotope expect the drug to lower the amount of lipid peroxidation, restore normal mitochondrial function and prevent mitochondrial cell death once distributed as an essential fat throughout tissues of the body.



Netarsudil -
treatment of
open-angle
glaucoma



Pimavanserin to
decrease
neurodegenerative
symptoms



RT001 in subjects
with **Friedreich's
Ataxia**



**Loss of
Proteostasis**



**Loss of
Proteostasis**



**Altered
Intercellular
Communication**

Completed Phase III Clinical Trials

GenSight Biologics is a gene therapy company specializing in treating severe inherited retinal and central nervous system diseases. Its two main products (GS010 and GS030) are designed to treat rare diseases, such as Leber Hereditary Optic Neuropathy (LHON) and Retinitis Pigmentosa (RP).

GS010 accounts for 87.5% of clinical trials conducted by GenSight Biologics in this area, GS030 - 12.5%. Most of Phase III clinical trials were conducted in the USA (87.5%), previous clinical trials were conducted in France (12.5%).

A third Phase III trial, pursuant to a special protocol assessment with the FDA, is the ongoing REFLECT study, which will evaluate the efficacy and safety of bilateral intravitreal injection of GS010 to treat vision loss up to 1 year.

GS010 passed Phase III Clinical Trials and demonstrated promising results in the treatment of Leber Hereditary Optic Neuropathy (LHON), an inherited mitochondrial genes disease of the eye that causes blindness.

December, 12, 2020

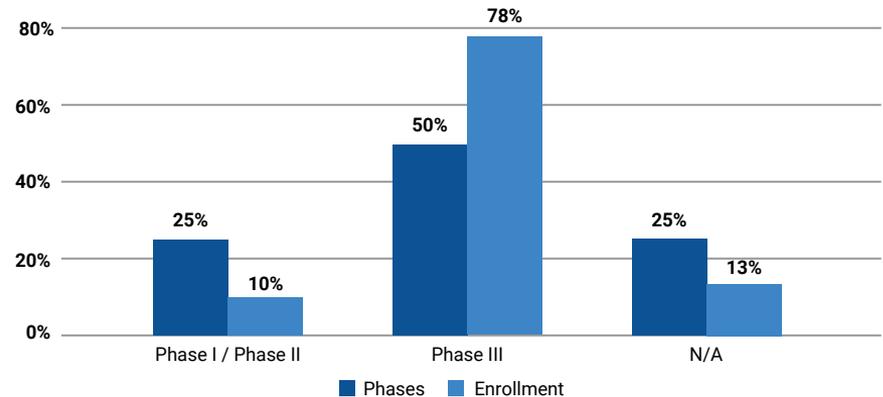
Sources: ClinicalTrials.gov, GenSight Biologics

Aging Analytics Agency



GS010 to treat the Leber Hereditary Optic Neuropathy

Distribution of the clinical trials GS010/GS030



GenSight reported key efficacy and safety results at 78 weeks post-treatment in the REFLECT Phase III clinical trial for LUMEVOQ®. The results show better visual acuity improvements from bilateral intravitreal injections of the gene therapy compared to a unilateral injection.

June, 30, 2021

Completed Phase III Clinical Trials

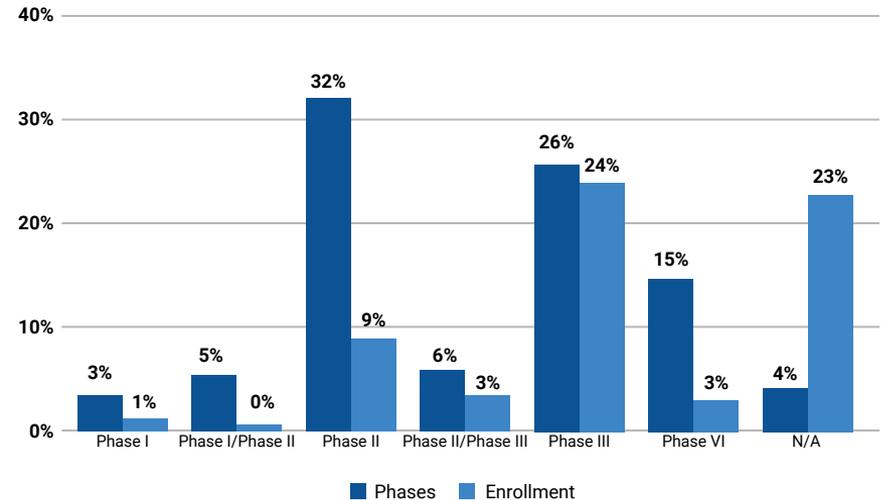
Grifols has developed **AMBAR**, a plasmapheresis technique that infuses patients with **human albumin** and **intravenous immunoglobulin (IVIG)** for the treatment of **Alzheimer's disease**. The company's hypothesis was that amyloid beta, the main driver of Alzheimer's disease, binds to albumin in the brain, which can then be removed from the body.

The company's results have confirmed that that this approach is valid, although it does not constitute a cure. In a **Phase 2b/3** trial, Grifols reports that treated patients with moderate Alzheimer's experienced a **61%** reduction in disease progression and a **71%** reduction of symptoms, with positive results reported for both moderate and mild Alzheimer's.

In **May 2021**, Grifols announced that the first center to offer the **AMBAR** procedure would open in Barcelona, Spain. Further centers in the EU, USA and China are planned.

Also in **2021** Grifols begins clinical trials of a new treatment **anti-SARS-CoV-2 immunoglobulin** that would provide immunity against COVID-19. At the moment, completed clinical trials occupy 62.4% and Recruiting – 18.8% (will end in 2022-2023). In clinical trials was attended by 29.4K people. In Phase III of testing 6.8K people, 91.3% fall into the age groups from 18 to 80 years old. Most of the Phase III clinical trials were conducted in the USA (56.4%) and Canada (17.9%). Most of the clinical trials were related to developing biological interventions (65,1%) and drugs (7.2%).

Distribution of the Grifols' clinical trials



GRIFOLS

AMBAR: a plasmapheresis technique for the treatment of Alzheimer's disease



Altered Intercellular Communication

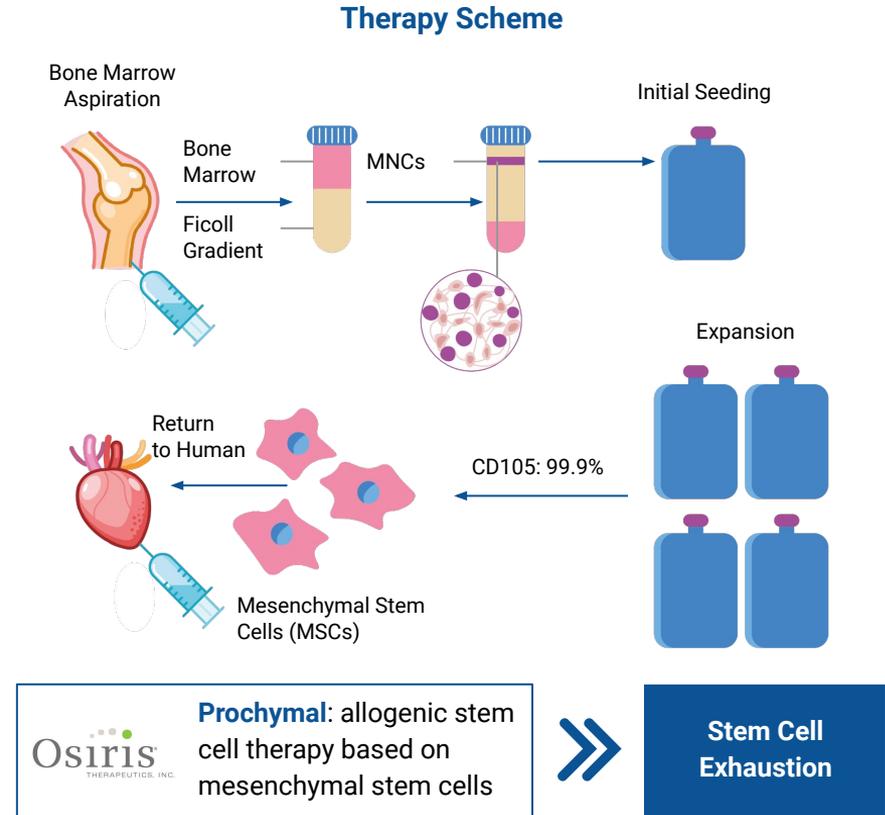
Completed Phase III Clinical Trials

Osiris Therapeutics has developed **Prochymal** - an allogenic stem cell therapy based on mesenchymal stem cells derived from bone marrow of donors aged between 18 and 30 years. MSCs are purified from the marrow afterwards cultured and packaged, with up to 10,000 doses derived from a single donor. The doses are stored frozen until needed. Administration of the product is mainly performed as infusion.

Stem cell therapies have multiple applications, but **Prochymal has clinically proved therapeutic effect on Crohn's Disease and Graft-versus-host disease (GvHD)**. First clinical approval of this drug happened in 2012, it was a first stem cell drug approved. The trials demonstrated that in 61 to 64% of children with acute GvHD who were unresponsive to steroids, Prochymal produced a clinically significant response at 28 days after the start of the therapy. Until the approval of Prochymal, there has not been any other effective therapy.

For present moment more clinical trials are on the way, the most recent progress is done in curing Acute Respiratory Distress Syndrome, Prochymal passed Phase II in this research.

Source: www.medicalnewstoday.com



Completed Phase III Clinical Trials

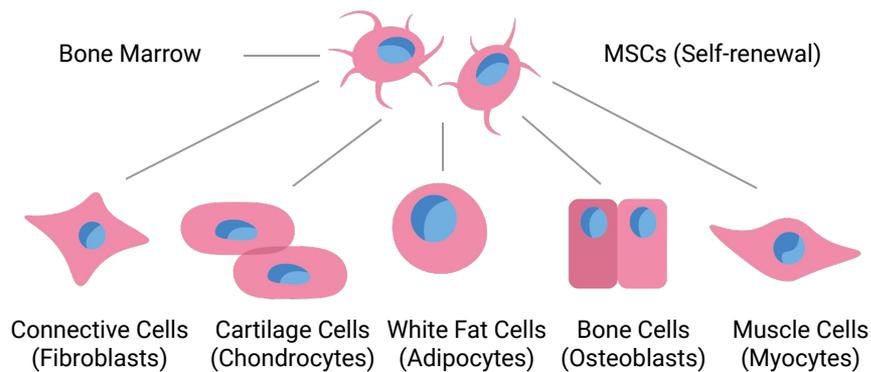
In 2021 **Mesoblast Ltd** has completed Phase III clinical study of **Rexlemestrocel-L**. This medication is Allogeneic STRO-3 immunoselected bone marrow-derived mesenchymal precursor cells that were used in treatment of Degenerative Disc Disease (DDD). It is an age-associated condition that represents Back pain caused by worn-down vertebral discs. Disc degeneration and associated low-back pain are major causes of suffering and disability.

Rexlemestrocel-L consists of a unit dose of 6 million mesenchymal precursor cells (MPCs). It is injected by syringe directly into a targeted damaged disc in an outpatient procedure. This clinical trial proved that Rexlemestrocel-L in low doses is improving function of spine and reduces pain syndrome through 24 months post-treatment.

Due to variety of possible stem cell proliferation fates therapies could have different applications. Thus Mesoblast Ltd is running clinical trials of the same medication in such vectors as: **therapy of Graft-versus-host disease, Myocardial infarction, Osteoarthritis, Rheumatoid arthritis, Spondylosis, Type 2 diabetes**. Trials which are now on Phase III are aimed to cure such conditions as: Acute myeloid leukaemia, Heart failure, Hodgkin's disease, Non-Hodgkin's lymphoma.

Source: adisinsight.springer.com

MSc Differentiation Options



 mesoblast

Rexlemestrocel-L: allogeneic stem cell therapy based on mesenchymal stem cells



Pain Management

Completed Phase III Clinical Trials

In spring of 2019, **Amgen** has completed Phase III clinical study of **proprotein convertase subtilisin/ kexin type 9 (PCSK9)**. It is a medication that was developed to downregulate systemic inflammation by decreasing the number of lipoproteins in blood. This protein plays a major regulatory role in cholesterol homeostasis, mainly by reducing metabolism of LDL-particles. PCSK9 is inactive when first synthesized, because a section of peptide chains blocks their activity; proprotein convertases remove that section to activate the enzyme.

PCSK9 binds to surface LDL sensing proteins which are responsible for endocytosis. In further cascade PCSK9 is activated when entering a lysosome leading to decomposition of LDL and its receptor whereas during natural endocytosis receptors are not decomposed.

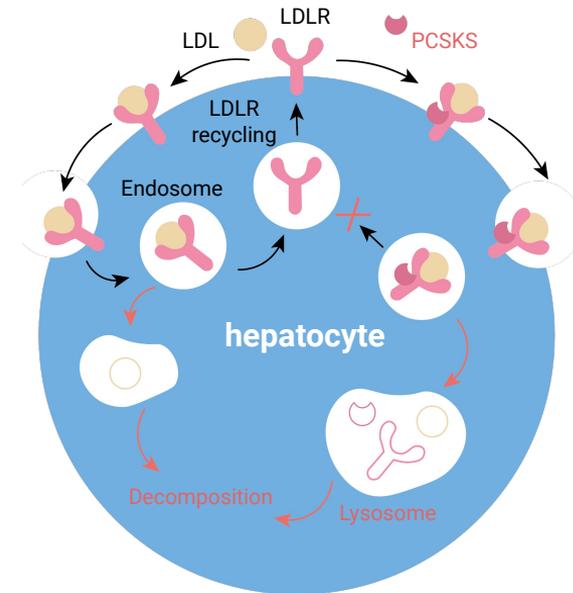
Administration of medicine is performed via injection once a month. Subject of this study was Hyperlipidemia but potentially this approach can manage other metabolism conditions, obesity and cardiovascular diseases.

On average, **PCSK9** treatment for 16 weeks resulted in a 17% reduction of circulating Lipids with 95% credible interval.

Source: clinicaltrials.gov

Aging Analytics Agency

Mechanism of PCSK9 Action



AMGEN

PCSK9: Metabolism normalization via endocytosis



Cell Signaling and Autophagy

Failed Clinical Trials

Most clinical trials related to Longevity face **huge risks of failure** because this **vector of study is relatively new**. But pioneers of such research are attracting more and more investors and public interest, thus potentially benefiting all upcoming research in this field.

RTB101 is a small molecule inhibitor of the rapamycin complex 1 (TORC1), designed by Restorbio to improve immune function in elderly. First clinical trial of RTB10 was determined to combat respiratory tract infections in older people. The research did not meet its primary endpoint, and the company has stopped the development of RTB101 in this indication. Still drug candidate is being researched for other possible applications.

Conquering cellular senescence is seen to be one of the most important steps in combating aging. Since 2018, UNITY biotechnology have developed four unique drugs for this purpose. UNITY's lead candidate drug, **UBX0101**, is a unique senolytic small molecule inhibitor of protein interaction. This protein triggers apoptosis in senescent cells. But during phase II of trial UBX0101 turned out to be ineffective. In spite of first clinical trial failure UNITY is developing senolytic candidates for various other age-related diseases.

Failures of modern therapeutics in the sphere of Longevity are the normal course of things. Given the low global clinical trials success rate, it can be foreseen that this number will stay even lower for Longevity-related research. Nevertheless, all research in this vector is benefiting the whole field due to its overall ideological coherency.

| Company | Drug Candidate | Company | Drug Candidate |
|---|---|---|--|
|  | RTB101 - a small molecule inhibitor of the rapamycin complex 1 |  | UBX0101 - senolytic drug to eliminate senescent cells |
|  | Capromorelin drugs - reduce risks of becoming frail. |  | TXA127 - Angiotensin-1-7 modulates cell signaling |

Planned Clinical Trials

Due to the continuous expansion of research and intensive developments in cellular and molecular biology, more and more approaches and medications are beginning to appear as potential forms of **Longevity therapy**. The popularity of these approaches is not expected to decrease in the near future.

AgelessRx is a modern company that focuses its resources on developing a Longevity approach and making it accessible. Most of their products are dedicated to treating metabolic conditions; besides that, they also offer bioage tests. **One of the main product goals for that company is to start its own anti-aging cosmetic line.**

The National University of Singapore is conducting a human clinical trial of the effects of alpha-ketoglutarate on people aged 45 to 65, testing biomarkers of aging such as epigenetic clocks, pulse wave velocity, and inflammation. Experts believe that a lot of studies will be conducted adopting this idea.

MetroBiotech plans to increase cell work efficiency by altering cell aging cascades, thus improving human performance. The clinical part of the trial is scheduled for the year 2022. It is also estimated that 3,000+ people will participate.

Globally, research in this field and the emergence of novel ways of diagnostics are attracting many investments, thus expanding research horizons. Generally, **clinical trials focus on three key hallmarks: stem cell exhaustion, cellular senescence, cell signaling, and metabolism.** Most experts believe that the market interest distribution will stick with longevity clinical trials for a long time.

Source: clinicaltrials.gov

The Most Prominent Spheres for Future Research

Diagnostics of Aging

Stem Cell Transplantation

Senescent Cell Elimination

Alternative Signaling Potentiation of Immunity

Mitochondria Restoration

Metabolism Restoration, Supplements

NAD+ Therapy Effect on Mitochondrial Dysfunction

Market Trends



Market Trends

The graph clearly illustrates the primary trend - **the clinical trials market is growing annually by an average of 30%**. Recently, the increase in the number of clinical trials has been **provoked by the synergy of 4 key factors** - market trends.

Key Market Trends

Vaccine Trials on Rise

Remote Trials Increase

Clinical Trials Disruptions

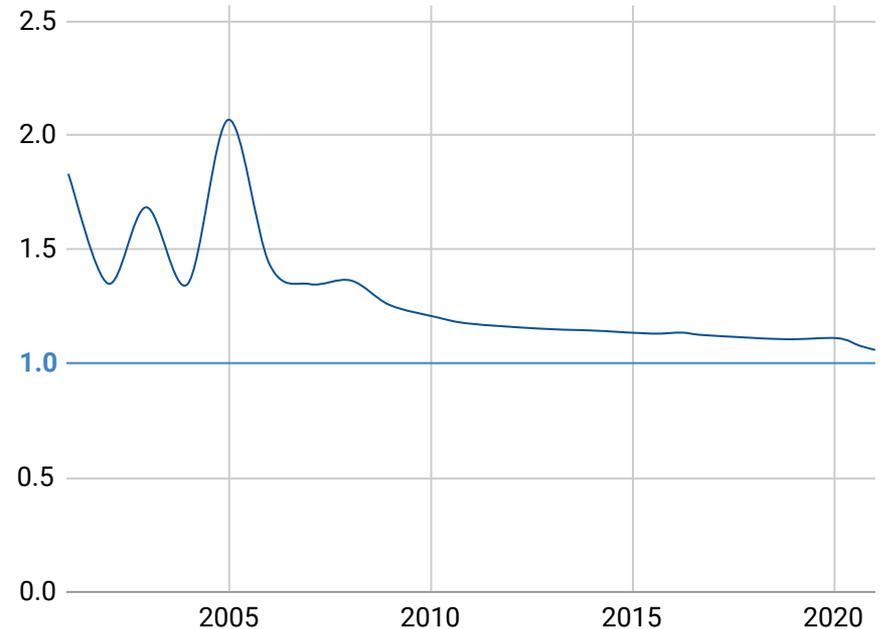
New Technologies in Clinical Trials

Determinant

COVID-19

Digitalization

Relative Increase in Clinical Trials, 2000-Q1 2021



Note: despite a precipitous drop in the number of clinical trials in 2005, the market continues to grow steadily as the relative increase is greater than 1.

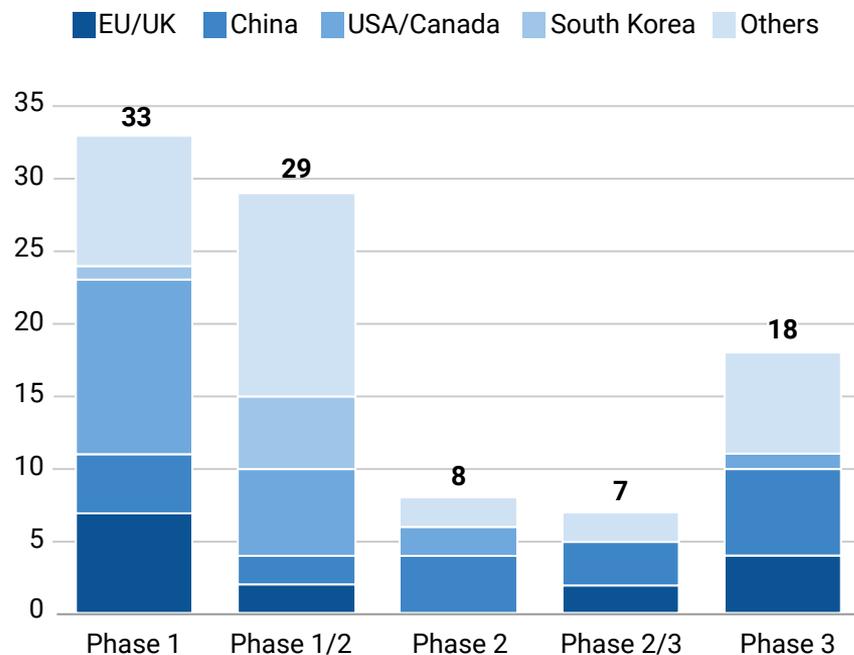
Vaccine Trials on Rise

Even though in some countries process of vaccination from COVID-19 is almost over, **more than 60 vaccines** are currently still listed for stage 1 or stage 1/2 trials, while **a whopping 184 candidates in pre-clinical trials** are registered with the WHO. 18 vaccines were presently listed by the WHO as being in stage 3 trials, among them shots already in use, like the Johnson & Johnson vaccine, both Sinopharm varieties, the Russian Sputnik and the Indian Bharat Biotech vaccine. On the other hand, only **five vaccines have progressed to phase 4**.

Moreover, **vaccines can increase longevity** by protecting against diseases that cannot be expected to benefit, thus affecting longevity.

Elderly individuals given the influenza vaccine in the USA had approximately **20% less chance** of suffering cardiovascular and cerebrovascular disease and **50% lower risk of mortality** from all causes than their unvaccinated counterparts.

COVID-19 Vaccine Pipeline Fills up Again, Q1 2021



Sources: COVID-19 Vaccine Pipeline Fills up Again, Vaccination greatly reduces disease, disability, death and inequity worldwide

Remote Trials Increase

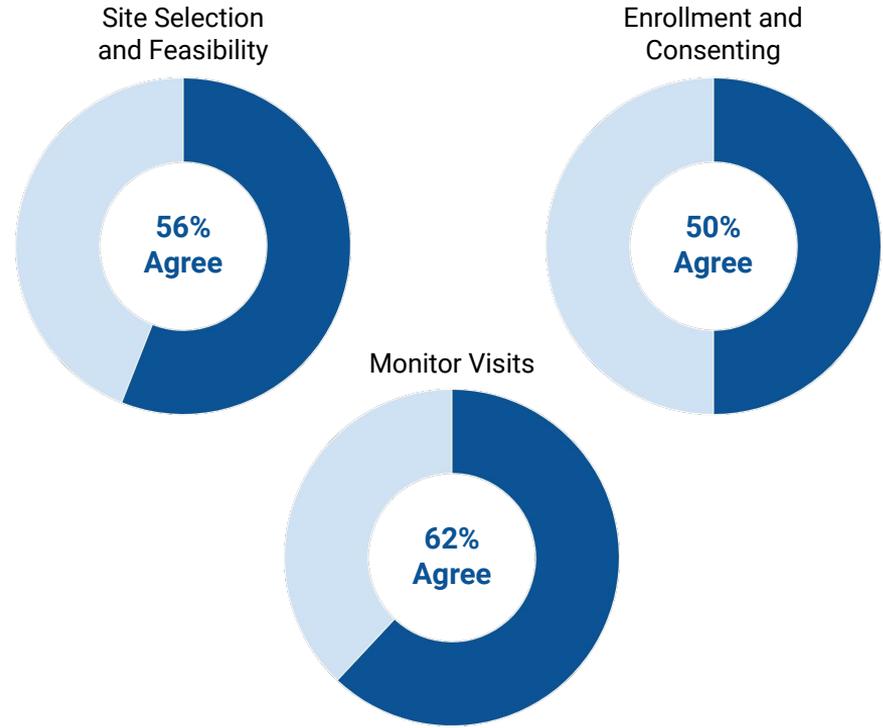
As the pandemic COVID-19 hit, **companies started to cut off additional costs and remove inefficient workflows.** In clinical trials, it was critical to the transition from on-site monitoring visits to remote site connectivity to ensure **efficiency, real-time oversight, and more timely data exchange.** As the demand for digital site connectivity is growing, both sites and sponsors expect over **fifty percent of all tasks to be completed digitally by 2023.**

Specially developed purpose-built systems that **support remote clinical trial monitoring** create cross-organizational efficiencies when the technology vendor considers both sites and sponsors' workflow needs. At the same time, additional workload, disjointed processes, and numerous portal logins for various sponsors are introduced.

Remote Clinical Trial Monitoring Benefits include standardized automatic data collection and storing, instant integration between systems, continuing tracking and efficiency, and reducing travel costs.

Source: Why Remote Clinical Trial Monitoring is the New Standard

Sites and Sponsors Expectations



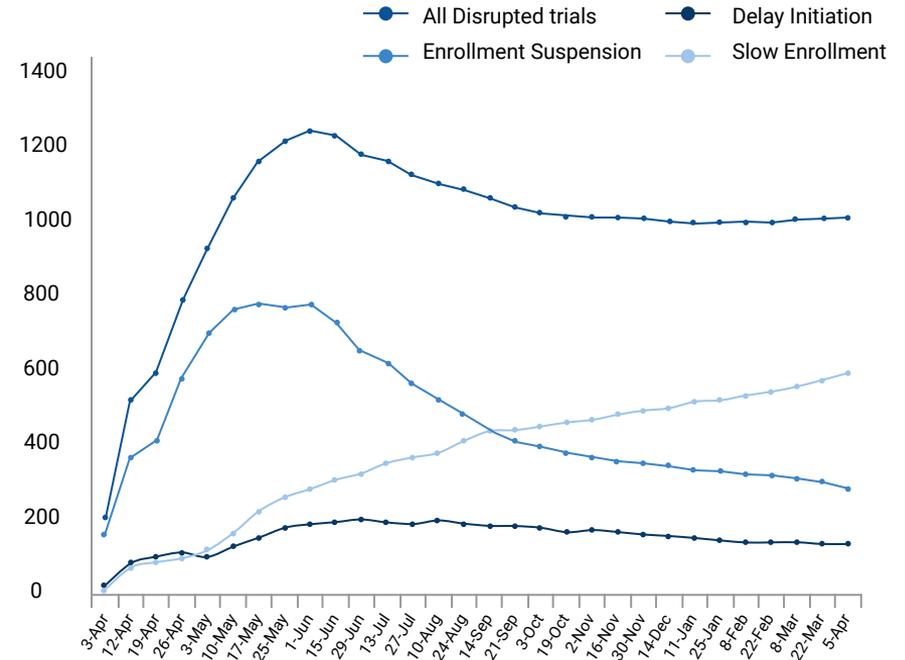
Clinical Trials Disruptions

The pandemic has had a **significant impact on the infrastructure of clinical trials**, from the countless staff furloughed or working remotely to the many labs and research institutions that have had to close temporarily. In addition, the effect of social distancing and the need to shield vulnerable patients has also led to trial suspensions at many sites.

The total number of disrupted trials has leveled off, but **the number of clinical trials that have resumed continues to rise**, although somewhat slower than the initial rise.

As the number of trials that have been impacted by slow enrollment continues to increase, this remains an issue. In addition, there is also a high risk to subjects in a clinical trial with a severe chronic or acute condition that affects their immune system, giving them a greater chance of contracting COVID-19 and making them unwilling to enroll in a clinical trial. Thus, companies and research groups are advised to overhaul the safety guidelines to attract more test subjects.

Global Clinical Trials Disrupted due to COVID-19, April 2020-April 2021



Sources: Clinical trial disruptions, Clinical trials continue to resume, GlobalData

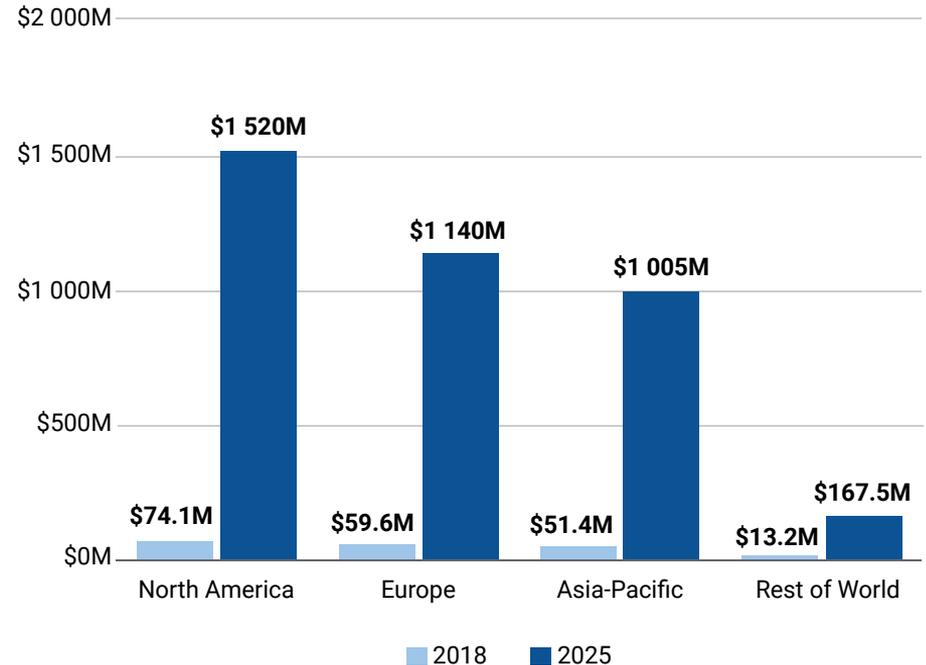
New Technologies in Clinical Trials

The biopharma industry is tied to clinical trials because of the constant competition. As a result, biopharma giants struggle to create new, more precise drugs reliably. **This implies a direct correlation between the use of AI in the biopharma industry and the use of new technologies in clinical trials.**

Global healthcare companies and governments are starting to catch up with **current trends in clinical trials**, starting from increasing engagement with digital ads ending with digitalized data collection, outsourcing more and more research to improve efficiency and decrease R&D costs.

The software technologies used will range from social media, mobile applications to AI-driven software solutions. One of the most widely used AI solutions currently underutilized on the market is in silico modeling that complements experimental research in a resource-efficient manner. It is predicted that **by 2025 the use of artificial intelligence in clinical trials will grow 15 times.**

AI Market in the Global Biopharma Industry in 2018 and a Projection for 2025, by Region



Sources: Digitalization of clinical trials , Artificial intelligence market in the global biopharma industry, Statista

Conclusions



Key Takeaways



The preclinical study is a stage of drug development that precedes clinical trials, and by the present protocol, is mostly conducted in animal models. However, it's becoming evident that the preclinical stage can now be partially transferred to in silico research. At its current state, this method is more reliable and resource-saving. Redefining the approach to preclinical studies is an upcoming event that will happen within ten years.



There are vanishingly few clinically validated drugs that reliably extend healthy human longevity. Clinical trials are less than 1% succeeding in humans after animal trials. At the same time, developments in AI and modeling sphere are pushing market to better results which promises further revision of research approach.



While clinical studies generally dominated the attention of investors, the global Preclinical Market Size is projected to grow an average CAGR of **8.1%** compared to only **5.9%** of clinical trials. The difference in growth can be explained by the USA **21st Century Cures Act, which accelerated the approval process for advanced drugs and medical devices.**



The global Preclinical Studies and Clinical Trials Market Size accounted for \$48.8B in 2020 and is projected to grow **an average CAGR of 6% from 2020 till 2026 to reach \$70.5B.** Despite increasing interest in recent years, the industry remains underestimated and has high growth potential.



The cost of developing a new drug increased tremendously in the last 50 years, **being up to 25 times higher in 2020s than in 1970s and is only projected to grow.** This partially explains a relatively new longevity drugs are in clinical trials pipeline.

Key Takeaways



While few of clinical trials examined dealt with aging directly, **the vast majority of clinical research is dealing with age-related conditions** due to higher market interest in precision drugs for specific disease. **Longevity trials** are focused on **increasing individuals lifespan and increasing life quality** at a later age. Most of them are now focused on fighting **cell senescence and restoring regenerative potential**.



Modern attitude to clinical trials is partially cocervative, some companies do not disclose information regarding their research to fortify their market position. That is why **any information database is not complete**. Current analytical case study is based on **self-prepared database consisting of all publically open trials**.



Out of nine recognized hallmarks of aging, only two, namely **altered intercellular communication and mitochondrial dysfunction, have drugs that passed onto Phase 3** of clinical trials. This means that while the need for such medicines is recognized, **the progress of obtaining viable products is still quite slow**.



The recent growth of clinical trial market is fueled by the synergy of 4 factors - **vaccine trials on rise, remote trials increase, clinical trials disruptions, and new technologies**. While first 2 market trends are projected to level off after the COVID-19 pandemic, the latter ones are here to stay, promising continued development of the industry.



Clinical trials is a continuously expanding field of scientific study. Although most of them do not bring successful results, the whole field of **modern therapeutics is based on their paradigm**. Lately, more and more innovative ways of conducting research in this field emerge, thus leading to potential reorganization of the whole process. **Enormous funding of drug development sphere** will persuade continuous progress and development as result, **requiring deeper analytics for precise overview**.

Possibilities for Further Improvements

Understanding that Clinical Trials Industry development is an **ongoing process** means that the project needs to be further improved. In particular, the second iteration of this analytical case study will improve on several aspects of the research approach.

The company, investor and R&D centers **database will be further expanded** to accommodate for rising startups and older companies pivoting towards expansion of their clinical trial rollout efforts. This will lead to increased selectivity of top 500 companies in the database.

Additionally, **deeper analysis on failed and planned trials as well as AI-based research** will be performed.

For broader understanding **law limitations and policies** on clinical trials in different countries will be assessed.

Profound research on products and treatment approaches will be expanded.

With several predictions about Clinical Trial Market trends being made, a follow-up is needed to recognize parts of the forecast that would turn out to be accurate, and further calibrate the methodology that allowed such predictions to be made.

Avenues for Further Improvement in the Second Iteration of the Project

Database Expansion

Further Integration of Biomarkers of Longevity

Updates on the Most Notable Clinical Trials

Follow-up on Predictions Made in the First Iteration

Increase Number of Deeply Studied Trials

Separate Research on Outsourcing Companies

Deep Analysis of AI Implementation

Broad Assessment of Failed or Planned Trials

Description of Law Limitation Difference in Countries



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