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FOREWORD

I am very pleased to welcome the readers of our Dementia in Europe magazine to this special supplement dedicated to clinical trials. Clinical trials are essential for the development of new ways to prevent, diagnose and treat dementia. As the number of people affected by dementia including Alzheimer's disease (AD) continues to rise, we hope you will share our interest and commitment to this important area of research.

In our previous edition published in 2019[1], we highlighted the complexity surrounding access to clinical trials, noting that information was not easily accessible for people wishing to participate in research. To address this, we introduced our Clinical Trials Watch, a user-friendly, web-based resource that consolidates up-to-date information on Phase II and Phase III clinical trials investigating drugs for the treatment of AD and other forms of dementia in an accessible and easy-to-understand format.

This 2024 supplement affirms our commitment to highlighting the pivotal role of clinical trials in dementia. The supplement begins with an introduction on the importance of clinical trials. Following this, you will find an overview of clinical trials in Europe, as well as a comparison with the clinical trial landscape in 2019. We also explore clinical trials for other forms of dementia. To expand our view, we have a comprehensive look at global clinical trials, assessing how Europe compares to other areas where AD research and clinical trials are being conducted. Looking at some of the practical challenges, we explore the barriers to participation and the innovative solutions being implemented to improve access to and availability of clinical trials.

Despite the hurdles, the progress made in recent years gives us reason for optimism. Notable advancements have been achieved recently with anti-amyloid therapies representing a new hope for people with AD. This supplement also features our position adopted earlier this year calling for concrete actions to enable timely, safe and equitable access to anti-amyloid drugs for patients who are most likely to benefit from these innovative new treatments for AD.

Finally, we feature the European Alzheimer's Disease Consortium (EADC), showcasing the collaborative efforts of this initiative in advancing scientific research on AD and related dementias.

Alzheimer Europe remains committed to a holistic approach to AD and other types of dementia where innovative new treatments are included alongside counselling, support and adequate care of people with dementia and their carers throughout the disease process.

We hope this supplement provides valuable insights into the current landscape of clinical trials for AD, inspiring continued research and collaboration in this critical field.

I want to acknowledge the contribution of the people involved in this work. My thanks go to Cindy Birck, Project Officer, and Angela Bradshaw, Director for Research, at Alzheimer Europe, who both wrote this report. I would also like to thank the European Group of People with Dementia (EWGPWD), the European Dementia Carers Working Group (EDCWG) and the pharmaceutical companies who provide insightful feedback on our Clinical Trials Watch.

Jean Georges,
Executive Director,
Alzheimer Europe

> "Alzheimer Europe remains committed to a holistic approach to Alzheimer's disease and other types of dementia where innovative new treatments are included alongside counselling, support and adequate care of people with dementia and their carers throughout the disease process".

Understanding clinical trials

The importance of clinical trials

Clinical trials are a type of research conducted with human participants aimed at evaluating the safety, efficacy and overall outcomes of medical approaches such as treatments, drugs, devices, behavioural interventions or surgical procedures.

Clinical trials are the cornerstone of medical advancement, playing a crucial role in the development and validation of new medical treatments/procedures and for obtaining regulatory approval for their use. Clinical trials may also test ways to detect and diagnose diseases and to better care for those living with diseases. Their importance can be highlighted in several key areas (Figure 1).

Phases of clinical trials

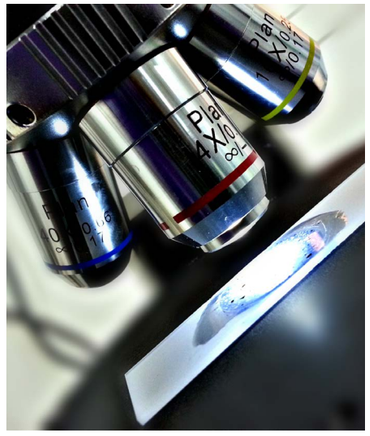
The journey of a clinical trial begins with preclinical research, where promising drugs and processes are identified. These drugs then enter several phases of testing, typically conducted in four phases, each with specific goals and characteristics:

- Phase 1: assess the safety of the treatment, including the optimal dosing and potential side effects in a small group of participants (20-100), often conducted with healthy volunteers
- Phase 2: evaluate the efficacy and further evaluate safety in a larger group of participants (100-300) who have the disease/condition that the drug is intended to treat
- Phase 3: confirm the treatment's effectiveness, monitor side effects and collect data for regulatory approval on a large group of participants (1,000-3,000)
- Phase 4: also known as post marketing studies, to gather additional information on the treatment's long-term effects, benefits and risks post-approval.

Relevance in the field of Alzheimer's disease

In Europe, around 9 million people are living with Alzheimer's disease (AD), and this number is expected to exceed 14 million by 2050. Despite the availability of drugs that can alleviate symptoms for some individuals, there is currently no preventative or curative treatment for AD in Europe. Several promising areas of research and advancements have recently emerged in AD clinical trials:

- Disease-modifying therapies: Trials investigating treatments aimed at altering the disease course rather than merely alleviating symptoms. This includes drugs targeting amyloid plaques and tau tangles, the pathological hallmarks of AD
- Biomarker and early detection: Advances in biomarkers that can facilitate early diagnosis and allow participants to be enrolled at the presymptomatic or early stages of AD, where interventions might be more effective



- Lifestyle and prevention trials: Studies are examining the impact of lifestyle factors, such as diet, exercise and cognitive training, on AD risk and progression (e.g. FINGER study)
- Genetic research: Investigations into genetic risk factors (e.g. APOE ε4) on disease development and treatment response, paving the way for personalised medicine approaches.

The relevance of clinical trials in AD cannot be overstated. Now more than ever, it is crucial to continue research for AD and other dementias. As the number of people affected by AD continues to rise, clinical trials are essential for finding effective therapies that can alleviate the impact of this condition and also make advances in early diagnosis and preventive measures.

1 Developing new or improving treatments
- Translate scientific discoveries from the laboratory into effective treatments for patients
- Identify and validate new drugs, therapies and preventive measures

2 Ensuring safety and efficacy
- Identify potential side effects and risks, leading to safer treatments
- Protect people and ensure that only treatments with a favourable benefit-risk ratio are approved for use

3 Advancing science
- Gain insights into the underlying causes and progression of diseases
- Leading to further innovations and continuous improvement of healthcare practices

4 Improving patient care and outcomes
- Test new treatments and compare them to existing standards of care to identify the most effective interventions
- Enhance diagnostic tools, caregiving strategies and overall quality of life for patients and their families

5 Ethical responsibilities
- Ensure that new treatments are tested in a controlled and systematic manner
- Help protect participants' rights and ensure that the research conducted is of high scientific integrity

Figure 1: The importance of clinical trials in advancing research

Current landscape of dementia trials in Europe

The landscape of dementia clinical trials in Europe is focused on Alzheimer's disease (AD), the most common form of dementia. This section provides an overview of the current state of AD-focused dementia trials in Europe.

Alzheimer's disease drug development in Europe

According to data from clinical trial registries, Europe has approximately 50 active AD clinical trials investigating various aspects of AD treatment, spanning all phases of drug development.

The below section focuses on Phase II and III clinical trials currently recruiting participants for the treatment of AD in Europe. We identified 24 Phase II and 14 Phase III trials investigating respectively 24 and 10 different drugs. The focus of these trials spans a variety of mechanisms of action, with an emphasis on disease-modifying treatments that aim to alter the underlying pathophysiology of AD. Figure 2 provides a detailed breakdown of the mechanisms of action of the agents currently in Phase II and III trials in Europe. The distribution highlights the diverse approaches being investigated, with a notable concentration on innovative strategies aimed at neuroprotection, neurotransmission and reducing inflammation. Concurrently, a third of the trials are targeting misfolded proteins, such as amyloid-beta and tau.

AD begins many years before symptoms become apparent and develops gradually over time. Progression along a continuum from presymptomatic AD (in which there are abnormal changes in the brain) to symptomatic Alzheimer's dementia (marked in addition by changes in cognition and functioning) tends to be slow and subtle. Mild Cognitive Impairment (MCI) is often considered as the stage between the expected cognitive decline of normal ageing and the more significant decline of dementia. MCI due to AD on the other hand, is considered to be the earliest symptomatic stage of AD. AD is most frequently diagnosed when people already have dementia and typically progresses in three stages: referred to as mild, moderate and severe.

As indicated in the Figure 3, the majority of clinical trials focus on populations with MCI and mild dementia due to AD, often referred to as early AD. However, Phase III trials also address important aspects of AD management, including the treatment of agitation and psychosis associated with AD. These trials aim to not only alter the disease course but also improve the overall quality of life for people at various stages of AD.

It is possible to rank European countries as indicated in Figure 4, which shows the number of active Phase II and III clinical trials recruiting participants in Europe. There are significant differences between European countries in terms of number of clinical trials open for recruitment. There is no country where it is possible for participants to enroll in all identified recruiting trials. UK, Spain, Germany, Netherlands, Poland and France are among the countries with most clinical trials. In a number of small and mostly eastern countries (e.g. Albania, Cyprus, Estonia, Iceland, Jersey, Latvia, Luxembourg, Malta), it is impossible for volunteers to take part in a clinical trial.

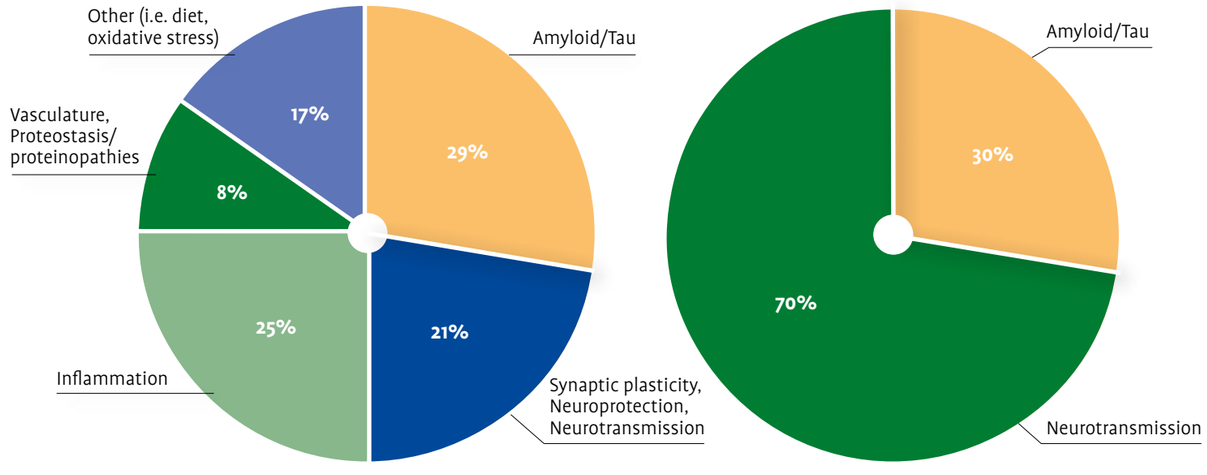


Figure 2: Mechanisms of action and biological targets for drugs in Phase II (left) and III (right) clinical trials

Current landscape of dementia trials in Europe

Recent advances in Alzheimer's disease clinical trials

The landscape of clinical trials for AD in Europe has evolved significantly between 2019, when our first supplement dedicated to AD clinical trials was published, and 2024. This section provides a comparative analysis of the number and nature of clinical trials between these two periods.

In 2019, AD clinical trials in Europe were characterised by a focus on amyloid-targeting therapies, following the amyloid hypothesis, which posits that amyloid-beta plaques in the brain are a primary driver of AD pathology. Several trials were underway, including those investigating monoclonal antibodies such as aducanumab and gantenerumab. Despite the high hopes, many of these trials faced setbacks, with some studies being halted due to lack of efficacy. Additionally, there was a strong emphasis on early AD.

The comparison between 2019 and 2024 shows a significant increase in the number of clinical trials for AD and other forms of dementia in Europe (Figure 5), reflecting advancements in scientific understanding and therapeutic approaches. By 2024, the focus of AD research in Europe had diversified significantly. While amyloid-targeting therapies continue to be explored, there was a marked shift towards other mechanisms, including tau protein targeting, neuroinflammation, synaptic health and neuroprotection (Figure 2). The most common processes targeted in Phase III trials include neurotransmitter receptors.

There are now more clinical trials being conducted across an increasing number of European countries. In terms of location, clinical trials were conducted across 22 European countries in 2019 (11 eligible countries for Phase II and 19 eligible countries for Phase III trials), compared to 27 countries in 2024 (19 eligible countries for Phase II and 22 eligible countries for Phase III trials), reflecting a broader and more inclusive effort in AD research and drug development.

Several countries have become active in hosting Phase II and III trials, including Estonia, Greece, Ireland, Israel, Norway, Slovakia, Slovenia and Switzerland. The inclusion of these countries marks a positive step towards a more comprehensive European research network, allowing for greater participation. However, Lithuania, Russia and Ukraine are no longer hosting clinical trials. While the inclusion of new countries is promising, disparities remain.

Clinical trials for non-AD dementias

While AD remains the most common form of dementia, other types, such as vascular dementia, frontotemporal dementia (FTD) and Lewy body dementia, also exist. Clinical trials for these other types of dementia are crucial for developing targeted treatments and improving patient outcomes. For example, given the strong genetic component of FTD, several trials are now exploring the role of genetic mutations and therapies targeting these specific genetic abnormalities are being developed.

In 2019, there were fewer trials for non-AD dementias in Europe (e.g., three active trials looking at agitation associated with dementia). However, there has been a growing number of trials targeting other forms of dementia over the past years (five active trials looking at agitation, psychosis and FTD, plus many trials that are no longer recruiting participants or have been completed), although they still represent a lower percentage compared to AD-focused trials.

Non-pharmaceutical sponsored trials, often led by academic institutions or governmental bodies, also play a vital role in dementia research. Although not well represented, these trials frequently explore innovative approaches and focus on a broad range of interventions, including dietary changes, cognitive training and psychosocial support.

Over the past years, we also noted an emergence of trials focused on repurposing drugs, which offer a promising avenue for dementia research. This approach leverages known safety profiles and mechanisms of action, potentially accelerating the availability of effective treatments. Current examples include anti-inflammatory drugs, antihypertensives and antidiabetic drugs.

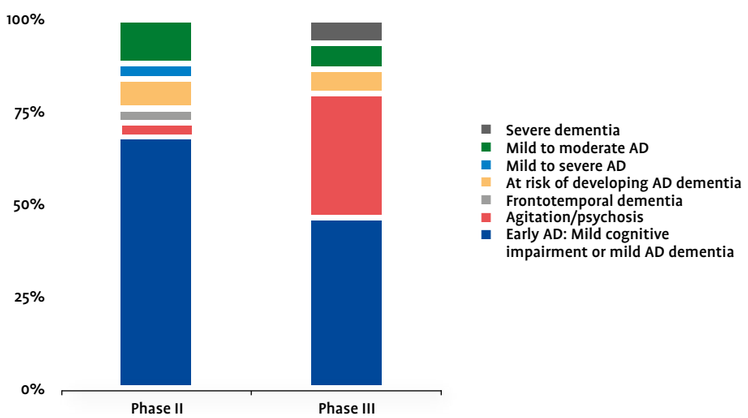
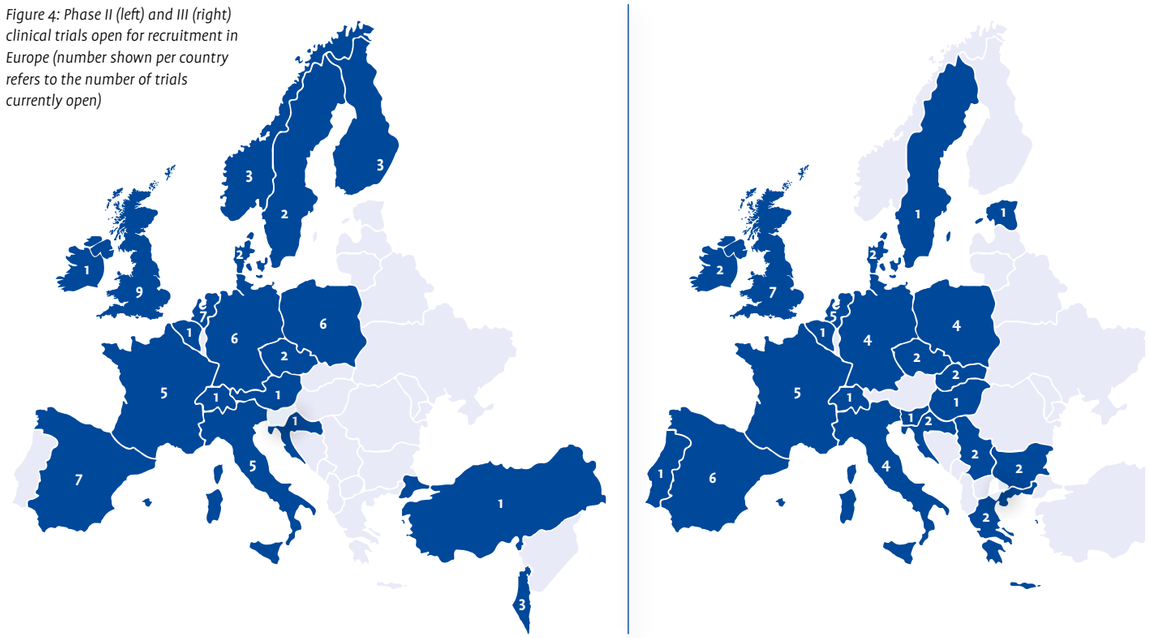


Figure 3: Distribution of Phase II and III clinical trials by AD stage and/or disease target

Figure 4: Phase II (left) and III (right) clinical trials open for recruitment in Europe (number shown per country refers to the number of trials currently open)



Clinical Trials Watch

The Clinical Trials Watch (CTW) is a user-friendly, web-based resource launched in 2016 by Alzheimer Europe. It provides up-to-date information on Phase II and III clinical trials investigating drugs for the treatment and prevention of AD and other forms of dementia in an accessible format.

This service aims to offer a comprehensive view of ongoing trials, though it is not an exhaustive list. All the clinical trials included are currently recruiting participants in at least one European country. However, it is important to bear in mind that recruitment may not happen in all countries at the same time. The content is updated regularly, based on information available on public registries.

For this resource, Alzheimer Europe collaborates closely with members of its European Working Group of People with Dementia (EWGPWD) and European Dementia Carers Working Group (EDCWG) to ensure that the information provided is understandable for a lay person, regardless of whether the person has a diagnosis of dementia, or not. Pharmaceutical companies and study sponsors are also asked to provide feedback to ensure the scientific accuracy of the information provided in the database.

The CTW was developed eight years ago and 118 clinical trials have already been reported via this service (37 in 2019). Although some trials have been removed since they are no longer recruiting participants, new trials have also been added, resulting in 24 Phase II and 14 Phase III clinical trials currently reported in the database (Q3 2024).

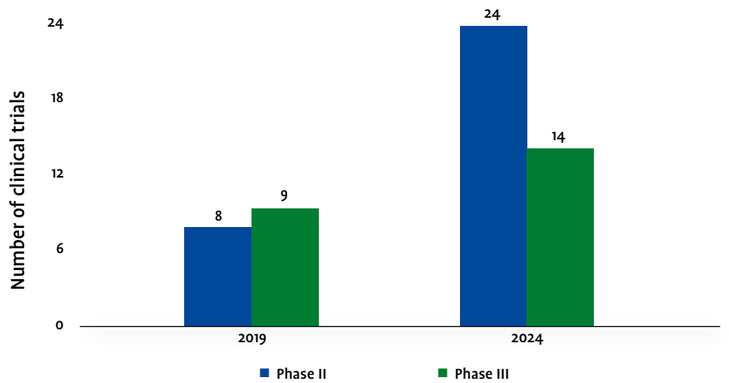


Figure 5: Comparison of number of active Phase II and III clinical trials currently recruiting participants in Europe: 2019 vs 2024

Global clinical trials for Alzheimer's disease

Alzheimer's disease (AD) research is a global endeavour, with numerous clinical trials being conducted worldwide. This section provides an overview of the current landscape of global clinical trials in AD, highlighting key trends and comparing Europe with other regions involved in AD studies.

Global AD drug development pipeline

According to the "Alzheimer's Disease Drug Development Pipeline: 2024"[2] there are 164 clinical trials assessing 127 drugs in the 2024 AD development pipeline. Data were obtained from Clinicaltrials.gov on active and planned Phase I, II and III clinical trials for AD, dementia and Mild Cognitive Impairment worldwide (index data was 1 January 2024). This includes 48 trials testing 32 drugs in Phase III; 90 trials assessing 81 drugs in Phase II; and 26 trials testing 25 drugs in Phase I. Most of the drugs in the AD drug development pipeline are disease-modifying therapies (DMTs). In total, there are 96 DMTs representing 76% of drugs in clinical trials and 31 symptomatic agents in the AD pipeline. Recruitment continues to be a challenge, with the average recruitment time for various trials stretching more than two years. Finally, the annual pipeline report highlighted that there are fewer trials, fewer drugs and fewer new chemical entities compared to the 2023 AD pipeline.

Funding

Regarding funding sources, a research article[3] noted that from 2016 to 2020, the number of AD clinical trials sponsored solely by biopharmaceutical companies (outside of public-private partnerships) decreased. However, according to the "Alzheimer's Disease Drug Development Pipeline: 2024"[2], 58% of all the trials in development are industry sponsored, up nearly 8% over the past year. This shift indicates a growing commitment from the pharmaceutical industry to advance AD research through increased funding and participation in clinical trials.

Global clinical trial distribution

According to the "Alzheimer's Disease Drug Development Pipeline: 2024"[2], of the trials with location recorded, 46% are conducted in North America only, 31% are conducted globally with both North American and non-North American sites, and 23% are conducted outside of North America with no North American sites participating.

We completed a search on Clinicaltrials.gov looking at active trials for AD in Phase I, II and III currently recruiting and enrolling participants by invitation (Q3 2024). We found that more trials are conducted in the US than in any other global region (Figure 6). While Europe remains a key participant, it faces specific challenges that impact its competitiveness compared to other regions.

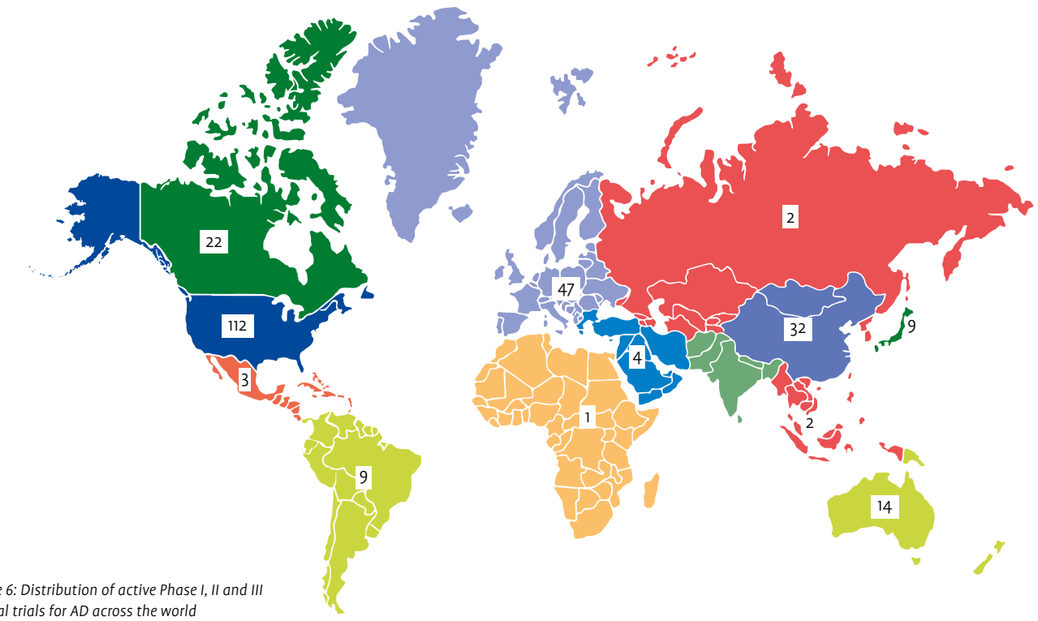


Figure 6: Distribution of active Phase I, II and III clinical trials for AD across the world

The Alzheimer Europe position on anti-amyloid therapies

In January 2024, Alzheimer Europe launched a new position paper on anti-amyloid therapies for Alzheimer's disease (AD), calling for concrete actions to ensure safe, timely and equitable access to these innovative medicines for all people with early AD who could benefit from treatment[4].

The growing prevalence and impact of AD has catalysed huge investments in research on its causes, diagnosis, treatment and care. After many high-profile failures, recent clinical trials of anti-amyloid drugs have marked a turning point for the field, leading to the approval of the first disease-modifying therapies for AD in the US, Japan, China, and other global regions.

Anti-amyloid drugs represent a new hope for many people with AD, with the potential to slow the progressive, clinical decline associated with the disease. However, the benefits and risks of treatment are multifaceted and complex, as are the findings from high-profile clinical trials of drugs such as lecanemab and donanemab. Although clinical trials have shown small, but statistically significant slowing of cognitive decline, treatment can cause side effects including brain swelling and micro-bleeds. Access to these innovative drugs will pose a major challenge, as inadequate resourcing of European healthcare systems excludes many from accessing a timely diagnosis, as well as patient-centred support, care and treatments.

The Alzheimer Europe position[4] was developed following engagement with its national members and the European Working Group of People with Dementia. Together, we identified three priority areas to support equitable access to anti-amyloid therapies. Firstly, accurate communication of the benefits and risks of anti-amyloid drugs is crucial, to enable informed, supported decision-making for patients and their families. Secondly, people with AD should receive an accurate and timely diagnosis, regardless of ethnicity, socio-economic status, language, or geographic location. Finally, European healthcare systems must make concrete infrastructure and workforce investments, to prepare for a future where disease-modifying therapies should be readily accessible to all patients who could benefit.

To address these challenges, Alzheimer Europe called for concrete actions from industry, regulators, payers, healthcare systems and governments. These include: accessible, inclusive communication of the benefits and risks of anti-amyloid drugs; the adoption of sustainable pricing policies; reimbursement frameworks that reflect the true value of treatment for patients and society without impacting the coverage of existing dementia treatments; and implementation of clinical pathways which support the diagnosis and treatment of AD in the early stages of disease, integrated alongside existing pathways focused on managing the symptoms of later-stage dementia.

Anti-Amyloid Therapies

Anti-amyloid therapies are antibodies that work by attaching to beta-amyloid, a protein that accumulates into plaques within the brain during the development of AD. This stimulates the immune system to clear amyloid plaques from the brain. There are a number of anti-amyloid drugs in development, which target beta-amyloid at a different stages of plaque formation.

Aducanumab (selectively targets amyloid aggregates)

March 2019: ENGAGE and EMERGE trials are terminated early
July 2020: Based on additional analyses of clinical trial results, Biogen submits marketing authorisation application to FDA
October 2020: Biogen submits marketing authorisation application to EMA
June 2021: FDA approves aducanumab under the accelerated approval pathway
December 2021: EMA rejects the marketing authorisation application for aducanumab; Biogen appeals the decision
April 2022: Biogen withdraws the EMA marketing authorisation for aducanumab
January 2024: Biogen discontinues development and commercialisation of aducanumab

Lecanemab (selectively targets soluble amyloid protofibrils)

May 2022: Biogen submits marketing authorisation application to FDA
November 2022: Positive results of Phase III Clarity-AD trial published
January 2023: Biogen submits marketing authorisation application to EMA
January 2023: Accelerated approval granted by FDA
July 2023: FDA converts lecanemab to traditional approval, widening coverage by US payers
July 2024: EMA rejects the marketing authorisation application for lecanemab: Eisai appeals the decision
August 2024: Approval of lecanemab by the UK's Medicines and Healthcare products Regulatory Agency (MHRA)

Donanemab (selectively targets an amyloid species that is enriched in plaques)

March 2021: Positive results of Phase II TRAILBLAZER-ALZ trial published
October 2021: Eli Lilly submits marketing authorisation application to FDA, for accelerated approval
January 2023: FDA rejects application for accelerated approval, citing insufficient participant numbers
April 2023: Eli Lilly submits marketing authorisation approval to FDA, for traditional approval
July 2023: Positive results of Phase III TRAILBLAZER-ALZ2 trial published in JAMA
July 2024: FDA grants traditional approval

Addressing availability challenges in clinical trials

The availability of clinical trials for Alzheimer's disease (AD) presents significant challenges globally, with noticeable discrepancies between Europe and other regions. These differences could be influenced by several factors including regulatory environments, resource allocation, infrastructure and population diversity. Addressing these challenges requires a concerted effort from global health authorities, research institutions and funding bodies to ensure that clinical trials are conducted efficiently and effectively across the world.

Major regions involved in AD research include North America, Europe and Asia-Pacific. Non-European regions often provide a more ethnically diverse population for clinical trials, making these regions attractive locations for such studies. Additionally, some regions/countries boast specialised research centres and institutions with significant expertise in AD, further enhancing their appeal for conducting trials.

Jane Mahakian

The regulatory environment also plays a critical role in the conduct and availability of clinical trials. For instance, the US Food and Drug Administration (FDA) is known for completing regulatory reviews more quickly than the European Medicines Agency (EMA), which has a more rigorous and time-consuming process[5,6]. Even within Europe, clinical trials for AD are unevenly distributed (Figure 4). The European Dementia Monitor 2023[7] reported a clear East-West divide in the availability of clinical trials and the recognition of dementia as a policy priority. Europe's decentralised healthcare systems further complicate coordinated clinical trial efforts, as each country has its own health system and regulatory body.

"Despite significant strides in AD research, there are still disparities in the availability and accessibility of clinical trials in Europe, with certain countries benefitting less from the results of such advancements. This geographical imbalance is particularly evident in low-to middle-income countries like Armenia where such clinical trials have not yet been done. Bridging this gap by potentially replicating such trials in Armenia provides a pathway for risk reduction, prevention and treatment and the opportunity to contribute to vital research advancements", said Jane Mahakian, Founder of Alzheimer's Care Armenia.

The Asia-Pacific region, with its rapidly evolving research infrastructure, is emerging as a competitive player. Although not focused on AD, a 2023 joint report[8] by PwC India and the US-India Chamber of Commerce (USAIC) highlighted that India has the potential to increase clinical trials fivefold in the coming years, thanks to a diverse patient population, cost-efficient research infrastructures and new regulatory reforms. Currently, India contributes only 3% to global clinical trial participation (compared to 30% in the US) but these compelling factors suggest a significant growth potential.

New strategies have been implemented by the EMA to enhance the availability of clinical trials for AD in Europe, aiming to harmonise regulatory processes and foster cross-border collaboration such as the EU Clinical Trials Regulation (CTR) and the Accelerating Clinical Trials in the EU initiative (see page 15).

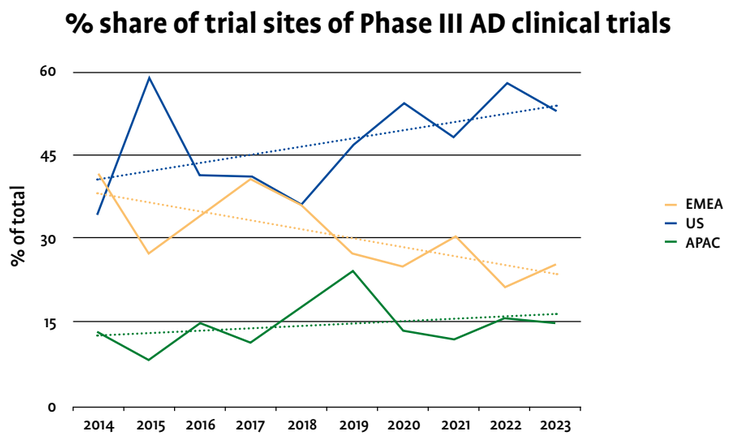


Figure 7: Comparison of Phase III trial site share in different regions 2014-2023
Data obtained from Clinicaltrials.gov on phase III industry sponsored clinical trials on AD in the past decade conducted worldwide, comparing the EMEA region (which here includes UK, Russia, middle East, and excludes African countries), the US and APAC (Asian Pacific region). Dotted lines depict graph trendlines.

Revitalising clinical trials in Europe: the sponsor's view

Patricia Paukovits

Patricia Paukovits, Medical Affairs Advisor, Neurology at Eli Lilly, shares the challenges faced by sponsors, but also explores ways to enhance the clinical development of Alzheimer's disease (AD) research in Europe.

Improvements in Europe's clinical trials environment are needed to make progress for patients today, especially for challenging conditions such as AD, where therapeutic options are limited and the burden on patients and caregivers continues to grow.

Public funding plays a crucial role in fostering innovation within the EU, yet the private sector's involvement, particularly in clinical development, is essential. The development of new medicines takes many years and is costly and risky, with a large proportion of drug candidates never reaching the market. The complexity and risks associated specifically with the final stages of clinical research demand substantial investments and operational capabilities. Some areas of clinical research fail more often than others, with AD being one of the riskiest with very low success rates and high costs. It is estimated that over the past 25 years, more than $24 billion has been spent on phase III AD clinical research[9].

One of the main challenges in AD research is finding treatments that are both effective in slowing disease progression and safe to administer. This complexity, combined with the low probability of achieving positive results, has led many pharmaceutical developers to abandon the field. However, recent progress has led to the identification of valid targets and biomarkers. This progress, coupled with refined clinical trial designs and execution strategies, has ended years of setbacks in the area, resulting in the first effective disease modifying drugs reaching the regulatory approval stage[10].

We have been active in the field for decades, and face specific challenges, because the pace of innovation in AD and its impact on clinical trial design is often confronted with inflexible trial implementation systems and capacity limitations. For example, the use of new biomarkers for AD diagnosis and disease progression monitoring requires substantial infrastructural and logistical adjustments, and not all regions are equally equipped to implement those. Although decentralised trials leverage "virtual" elements to facilitate patient participation and streamline trial processes, their implementation is constrained by strict data privacy rules, such as the General Data Protection Regulation. Additionally, diverse regulatory frameworks across EU countries delay the initiation of clinical trials. Securing approval to conduct a clinical trial across multiple EU countries can take a long time. For instance, under the new CTR, the median timeframe from submission to decision of a Clinical Trial Application (CTA) is approximately 115 days, compared to an average of 75 days for mono-national trials. In comparison, the FDA reviews original Investigational New Drug submissions within a 30-day window. If the CTA approval is given conditionally, with countries requiring substantial changes (e.g., clinical trial protocol), it can take even longer to start the trial. Faster processes, better harmonisation and more advanced infrastructure facilitate efficient patient enrolment and trial completion in regions outside of Europe. Extended approval timelines and complex regulatory processes contribute to a trend where Europe is increasingly being bypassed by other regions. The number of trial sites participating in industry sponsored Phase III AD clinical trials is decreasing in Europe (Figure 7), while other regions across the globe are increasing their investment in clinical research ecosystems. Given the timelines under the newly introduced CTA process, this is unlikely to improve.

After all, the most important rationale for investing in clinical innovation is to bring it to patients in a timely manner to improve patient outcomes and care.

To counter this trend and restore Europe's competitiveness in AD clinical trials, benefiting both patients and health systems, we would like to propose the following key actions:

- **Harmonise clinical trial approval processes and facilitate stakeholder cooperation i.e., sponsors, sites, regulators and Ethics Committees. This requires the creation of a more flexible and streamlined regulatory framework to address the complexities and rigidity in the submission and approval of clinical trial applications**
- **Collaborate to develop measures and propose changes to break down barriers and streamline and shorten processes**
- **Improve regulators resourcing, foster multistakeholder dialogue and promote flexible regulatory – industry interactions**
- **Cut red tape to enable cross-border access to clinical trials**
- **Develop new approaches to raise awareness and improve access to trials.**

Overcoming challenges in clinical trials accessibility

Clinical trials for Alzheimer's disease (AD) face significant challenges, from recruitment, retention and diagnosis to trial design and outcome measurement. Issues of availability and accessibility also pose major hurdles. Ensuring that trials are accessible to diverse populations is crucial for both participants and the success of these studies.

Chris Roberts

Enhancing clinical trial accessibility through user-friendly platforms

Many potential participants and caregivers remain unaware of available clinical trials due to limited public knowledge and complex information. This point was stressed in our 2019 Clinical Trials Supplement, where we stated that information about clinical trials is not readily accessible. Implementing user-friendly platforms can improve access by offering clear, understandable content and reducing technical language, making trial information more accessible to participants and caregivers.

"Taking part in research as an expert by experience means that you need correct information about all clinical trials that might be relevant, what is required and expected from all involved presented in a way that is accessible, easy to read and understand. That is exactly what Alzheimer Europe has produced with their dementia friendly resource on clinical trials.

The Clinical Trials Watch brings together up-to-date information on clinical trials investigating drugs for Alzheimer's disease and other dementias, in an accessible format", said Chris Roberts, member of the European Working Group of People with Dementia.

"Supporting people affected by dementia to engage in dementia research is vital to advancing our understanding of the condition, particularly in the areas of care, quality of life and symptom management. TeamUp for Dementia Research was created by The Alzheimer Society of Ireland (in conjunction with Dementia Research Network Ireland) to address a crucial gap in the dementia research ecosystem. The service provides an accessible and inclusive touchpoint for people affected by dementia, connecting them with research opportunities in a streamlined and person-centred manner. It further serves the dual purpose of offering vital recruitment support to researchers. By fostering greater participation in research, TeamUp for Dementia Research empowers individuals and their families to contribute meaningfully to the dementia research space, building a sense of hope and community.", said Cíara O'Reilly TeamUp for Dementia Research service manager.

Increasing innovations with digital technologies and decentralised trials

Clinical trials are often conducted at specialised research centres, which can be challenging for participants in rural and remote areas due to limited access and the burden of frequent travel. Recent advances in digital technologies and

Ciara O'Reilly

decentralised trials have opened a window of opportunity to introduce new methods into clinical trials, creating a more inclusive trial environment. These innovations address logistical and geographic barriers by bringing trial-related services closer to participants such as home visits for assessments and sample collection when feasible, and satellite sites deploying mobile clinics to reach participants in rural or underserved areas.

"Detecting subtle changes in cognition and daily life functioning in the earliest stages of Alzheimer's disease is challenging. Digital technologies that people wear or carry on their person every day, such as smartphones, smartwatches, and activity trackers, may provide a solution, as metrics derived from such devices may be sensitive enough to detect disease related changes. This hypothesis formed the basis of the pan-European RADAR-AD study, in which 230 patients across the Alzheimer spectrum and their caregivers were monitored remotely with a variety of devices for eight weeks.

Since accessing personal digital devices can be considered highly invasive by patients and comes with major privacy challenges, the RADAR-AD study team worked closely with the patient advisory board (PAB) coordinated by Alzheimer Europe to address these issues. This group was involved throughout the entire study and provided valuable input on the study design and execution. Thanks to this collaboration, the RADAR-AD study was highly successful in terms of recruitment and retention, with the majority of study participants successfully completing the study. The RADAR-AD study team is convinced that the contributions of the PAB demonstrated that people living

with dementia and their caregivers were willing to accept and incorporate new technologies into their daily lives", said Casper de Boer, member of the RADAR-AD project.

Ensuring accessibility for diverse populations

Participants in AD clinical trials are mostly from high-income countries and lack diversity, with underrepresentation of certain groups, including racial, ethnic and gender minorities, as well as individuals from lower socioeconomic backgrounds and with comorbidities. Achieving inclusive and diverse representation is essential for making the study population more reflective of all those affected by AD, allowing broader access to advancements in therapies.

Casper de Boer

A few words from representatives of national Alzheimer's associations

Magda Tsolaki

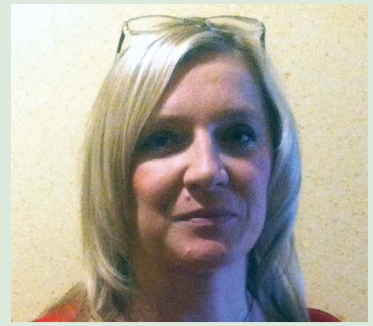
"Our participation in clinical trials for anti-amyloid drugs in Greece has been limited due to the absence of amyloid PET scans. We only have the option of lumbar punctures, which has naturally limited our involvement compared to other EU countries in such trials. Despite this, our efforts over the years have driven us to focus on other types of trials. For instance, we are now ready to start a study with people with Alzheimer's and Down syndrome. We have also completed trials and published findings on natural products such as saffron, extra virgin olive oil, and pomegranate seed oil[11,12,13].

This year, we explored spirulina, a tablet which is used by people who travel into space, showing improvements in some cognitive functions in people with mild dementia and mild cognitive impairment. The positive impact was evident as patients bought spirulina after the end of the study to continue using it. Although our studies are not multi-centre studies, I think that we have made significant progress.

We recognise the potential of natural products but face challenges in identifying the right combinations for disease prevention. We are committed to continued research to find the effective combination and advance our understanding of their benefits", said Magda Tsolaki, Chair of the Greek Association of Alzheimer's Disease and Related Disorders (Alzheimer Hellas).

"In Poland, clinical trials are conducted in two types of centres. The first type, which is historically more common, takes place in neurology or outpatient clinics. However, for several years now, restrictions have been introduced meaning that they must be conducted after doctors' working hours. The second type, which is becoming increasingly popular, takes place in clinical research centres, where clinical trials are conducted on drugs for various diseases. We also have separate clinical research centres, where only drugs for neurological diseases, including Alzheimer's disease, are tested.

In recent years, two types of clinical trials have become available. The first is those for people with Mild Cognitive Impairment (MCI), where the patients themselves give their consent to participate in a clinical trial. They are most often referred to a clinical trial by doctors to whom patients report their symptoms of memory disorders. It is also quite common for patients with MCI to report to clinical trials, which they learn about on the internet (e.g. through Facebook). The second type of clinical trial is agitation in Alzheimer's disease. These trials are usually initiated by physicians for patients showing signs of aggression and agitation. Recruitment for these trials is difficult, however, because the decision about the patient's participation rests with the caregiver, as the patient has difficulty with making informed decisions", said Edyta Ekwińska, Alzheimer Poland.



Edyta Ekwińska

Sponsor insights: Addressing accessibility challenges in clinical trials

Seeking to understand the true needs of people living with Alzheimer's disease (PLWA) and how to best support them; Roche established the Finding Alzheimer's Solutions Together (F.A.S.T.) Council, bringing together PLWA, care partners, as well as global and local Alzheimer's disease (AD) patient organisations. One of their objectives is to understand the key challenges in AD clinical trials and develop actionable recommendations to address them. The Council's work has resulted in several important reports, that are available as open source[14,15,16,17]. In the Clinical Trial guidebook[14], the F.A.S.T. Council reported key barriers to participation and retention in AD clinical trials. The council emphasised the need to rethink the design and delivery of these trials to better meet the needs of PLWA and their care partners. The guidebook aimed at identifying ways of improving clinical trial design and outcomes, such as the importance of enabling connection on a personal level with participants and study partners to foster trust, and providing practical support during a trial, like offering remote assessments where possible.

This was a first-of-its-kind initiative between the pharmaceutical industry and the wider AD community when published in 2022, in which PLWA and care partners collaborated as 'experts through experience'.

During further F.A.S.T. Council meetings, the importance of diversity, equity and inclusion (DE&I) in AD clinical trials was repeatedly identified. This led to the creation of a dedicated report on this topic in collaboration with DE&I and AD scientific experts[16], which recommends policy improvements to ensure DE&I in AD clinical trials. This report examines the implications of underrepresentation and proposes strategies to promote greater inclusivity.

A few words from Ruth Croney, Clinical Programme Leader, Roche

Why is it important to ensure that clinical trials meet the needs of people living with Alzheimer's disease and their study partners?

Ensuring that clinical trials meet the needs of PLWA and their study partners is crucial because these individuals face unique challenges that can significantly impact their participation and their ability to continue with all the study visits required. If these needs are not addressed, it can decrease the ability to reach a broader diverse representation of PLWA in our clinical trials, which ultimately can reduce treatment options for PLWA, those who are directly affected by the disease. These individuals, with their care partners, can truly provide insights on the benefits of potential treatments. Their experiences and feedback are invaluable in shaping trials that better answer the needs of participants/study partners, improving both the quality of the information collected and the overall success of the trials (which means a trial with positive results).

Ruth Croney

What are some of the main barriers to accessing clinical trials that you have identified in your research or experience?

Having access to a diagnosis still remains a challenge, and diagnostic tools in primary care are limited, as is information and education relating to clinical trials. Furthermore, we need to ensure that our education is tailored so that we can engage with a diverse population that represents the true demographics of the people who have the disease in the 'real world'. To reduce barriers and ensure inclusivity into clinical trials is achieved, there has to be recognition of how differing socio-determinants of health and individuals' life experiences influence trial participation and health care choices.

What future developments are planned to further enhance the diversity and equity of clinical trials?

We are planning initiatives to reduce burden and increase family support, where we operate with zero out of pocket expenses for clinical trial participants and their care partners. Also, our ambition is to implement accessible pre-screening (early identification of individuals who may be eligible for clinical trials) which can be managed with low clinical resources either at a medical facility or in the community setting (e.g. church or supermarket) with initiatives such as mobile research units. With such initiatives, we want to broaden access to clinical trials and generate insights from those who fall outside of our inclusion/exclusion criteria and how many of those are related to AD versus lifestyle factors (e.g. lack of care partners).

Another primary focus is to provide support for sites to increase the numbers of trained individuals who are able to perform rating assessments for clinical trials (which are our primary trial outcome measures) and to ensure there are training programmes for those who are either less experienced or from diverse communities. Roche has been collaborating with the National Institute for Healthcare Research (NIHR) UK-wide Rater programme recently, to support research raters so they can also obtain approval to deliver research scales on Roche AD clinical trials across the UK.

We are committed to continuing to work with the F.A.S.T Council to shape these strategies together, to foster a more equitable and inclusive research landscape in AD, and most importantly, to also share our learnings back to the community.

Legal frameworks: the Clinical Trials Regulation

The Clinical Trials Regulation

Clinical trials in the European Union (EU) are governed by the Clinical Trials Regulation (CTR)[18], which became applicable on 31 January 2022. This regulation aims to create an attractive and favourable environment for large-scale clinical research in the region while maintaining high standards of public transparency and safety for clinical trial participants.

Prior to the implementation of the CTR, clinical trial sponsors were required to submit clinical trial applications separately to national competent authorities and ethics committees in each European country to gain regulatory approval. This fragmented process was time-consuming and administratively burdensome. The CTR introduces a streamlined approach by enabling sponsors to submit a single online application via the Clinical Trials Information System (CTIS) platform for the approval of clinical trials in up to 30 European countries, significantly enhancing the efficiency of multinational trials.

The updated rules under the CTR are designed to increase transparency by improving access to clinical trials information for the general public, and to facilitate collaboration across the EU Member States. By centralising and simplifying the application process, the Regulation aims to attract more research and investment to Europe. This is expected to foster innovation and enable the conduct of larger clinical trials across multiple EU countries.

With the recent revamping of the CTIS public portal[19], key clinical trial information that is most relevant to patients is published early, bringing an unprecedented level of data sharing. The revised transparency rules in the CTIS are also meant to reduce administrative burden for public authorities and sponsors, while ensuring the protection of personal data and commercially confidential information. Finally, CTR benefits healthcare professionals as the CTIS platform is more user-friendly, facilitating access to information on clinical trials and enrolment in clinical trials.

"The centralised system of submitting, assessing, authorising, and making public information about clinical trials in the EU will be a very rich source," according to Peter Arlett, head of the Data Analytics and Methods Task Force at the European Medicines Agency (EMA), "not just for us as regulators, but also for companies, academics, and patients associations," he said in a recent article[20].

> "This project is designed to strengthen the European environment for clinical trials. It's an enormous opportunity to put Europe back on the map as a world-leading research environment"

Accelerating Clinical Trials in the EU

The Accelerating Clinical Trials in the EU (ACT EU) initiative[21] is a transformative effort launched in January 2022 by the European Commission (EC), the Heads of Medicines Agencies (HMA) and EMA. Building on the momentum of the CTR and the CTIS, ACT EU aims to further establish the EU as a competitive centre for innovative clinical trials.

ACT EU seeks to transform the way clinical trials are initiated, designed and conducted. The overarching goal is to promote the development of high-quality, safe and effective medicines while better integrating clinical research into the European health system. By doing so, the initiative aims to enhance the EU's global standing in clinical research and pharmaceutical innovation.

To achieve its objectives, ACT EU has identified 11 key priorities that form the backbone of its workplan[22]. Key priorities include, among others: 1) establishing a multi-stakeholder platform for the stakeholders involved, 2) supporting the modernisation of good clinical practice in order to align with the increasingly diverse range of clinical trial types and data sources, 3) supporting the implementation of the CTR, and 4) reinforcing scientific advice coordination between clinical trial approval and clinical trial design, so as to facilitate the development of safe and effective medicines.

"This project is designed to strengthen the European environment for clinical trials. It's an enormous opportunity to put Europe back on the map as a world-leading research environment", said Emer Cooke, EMA Executive Director, during a press conference.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) also welcomed the ACT EU initiative, stating in their press release[23] that this is "the beginning of an exciting new phase for clinical research in Europe".

Legal frameworks: the EU Pharmaceutical Legislation

Ursula von der Leyen's 2020 State of the Union address came at an unprecedented time for the European Union. Facing stark realities exposed by the ongoing COVID-19 pandemic, she called for the creation of a European Health Union, saying "We cannot wait for the end of the pandemic to repair and prepare for the future. We will build the foundations of a stronger European Health Union in which 27 countries work together to detect, prepare, and respond collectively." One of these foundations was a new, European, pharmaceutical strategy – touted by the European Commission as a patient-centred plan to ensure the quality, safety, availability and affordability of medicines across the EU.

The current EU legislation for medicines is set out in two Regulations (EU No.2019/6 and No.726/2004) and one Directive (2001/83/EC). Together, they provide a legal framework that governs the regulatory approval, manufacture, distribution and supervision of veterinary and human medicines in Europe. The last major revision to the general pharmaceutical legislation of the EU dates back to 2004. Six months after Ursula von der Leyen's address in the autumn of 2020, the Council of the European Union published its conclusions on access to medicines and medical devices, calling for closer cooperation between Member States and European institutions to ensure affordability, availability and access to medicines for people across Europe. Revision of the pharmaceutical legislation was announced in the 2022 Workplan of the European Commission, which includes the following text: "The revision of the general pharmaceutical legal framework aims to ensure access to quality, safe, efficacious and affordable medicines in the EU. It aims to foster innovation including in areas of unmet medical needs and to enhance security of supply while adapting to new scientific and technological developments and reducing regulatory burden where possible."

On April 26, 2023, after four years of thorough discussions, the European Commission unveiled its proposals for a comprehensive overhaul of the pharmaceutical legislation. The 2023 Commission proposal streamlined the laws governing medicines in Europe, creating a new Directive and Regulation to revise and replace Directives 2001/83/EC and 2009/35/EC, and Regulations 726/2004 and 141/2000, incorporating relevant aspects of the Paediatric Regulation (EC/1901/2006). With a stated goal of bolstering innovation in areas of unmet medical need, and addressing the issue of inequitable access to medicines across Europe, the legislative package included a number of proposed measures to stimulate innovation, address medicines shortages, and ensure earlier availability of generic and biosimilar medicines.

To stimulate innovation, the Commission proposed regulatory data protection incentives for companies developing medicines that tackle unmet medical needs, defined as "conditions for which there exists no satisfactory method of diagnosis, prevention or treatment". According to the 2023 proposal, companies could benefit from an additional 6 months of market exclusivity, with an extra year awarded for medicines that meet the criteria of high unmet clinical need. To encourage access, the Commission also offered a two-year extension of regulatory data protection for companies that make their products available in all 27 Member States.

However, the baseline regulatory data protection was reduced from 8 to 6 years compared to the 2004 pharmaceutical legislation – a change that was widely criticised as stifling innovation by reducing financial incentives to develop new treatments. The narrow definition of unmet clinical need was also criticised, with many patient groups calling for a more comprehensive approach that includes criteria such as quality of life for patients and caregivers.

The European Parliament

Following a year of intense negotiations and discussions, the European Parliament adopted its position on the proposed reforms in April 2024. During a plenary vote on 10 April, MEPs adopted the new Directive (495 votes in favour, 57 against and 45 abstentions) and Regulation (488 votes in favour, 67 against and 34 abstentions). Speaking to reporters after the plenary, Pernille Weiss (Parliament co-rapporteur for the pharmaceutical legislation reform) said "Today's vote is a step towards delivering the tools to tackle present and future healthcare challenges, particularly for our market attractiveness and access to medicine across EU countries."

A number of changes were made to the legislative package in response to feedback on the initial proposals from the European Commission. To address concerns about regulatory data protection, the Parliament proposed a minimum period during which other companies cannot access product data of seven and a half years, in addition to two years of market protection (during which generic, hybrid or biosimilar products cannot be sold), following marketing authorisation. Furthermore, pharmaceutical companies would be eligible for additional periods of data protection if their particular product addresses an unmet medical need (+12 months), if comparative clinical trials are being conducted on the product (+6 months), and if a significant share of the product's research and development takes place in the EU and at least partly in collaboration with EU research entities (+6 months). However, MEPs also imposed a cap on the combined data protection period of eight and half years. Discussions on the Commission's proposal are ongoing in the Council. Once the Council adopts its position, trilogue negotiations between the Commission, Parliament and Council will start.

The revision of the pharmaceutical legislation is a unique opportunity to improve and accelerate access to safe and effective medicines in Europe. To understand the patient and industry perspectives, we spoke to the European Patients' Forum (EPF) and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Andy Powrie-Smith, Communications Executive Director, EFPIA

The ongoing revision of the EU pharmaceutical legislation is critical for Europe's health. It is an opportunity to future-proof EU's legislative framework making us more competitive, helping Europe regain its position as a global leader in discovering, developing and delivering the latest advances in care.

Over the last thirty years Europe has lost a quarter of its share of global R&D investment to other more ambitious regions of the world. The revision is a chance to reverse some of these trends, strengthening rather than eroding Europe's intellectual property framework. This is crucial in areas like Alzheimer's disease, where the risks are high, and the rate of failure is significant. The original proposal by the European Commission weakens Europe's IP framework, making investment, the opportunity to participate in clinical trials, and access to cutting edge treatments less likely.

The revision also presents an opportunity to support small and medium-sized enterprises, often an engine room of advances in treatment. The future of innovative medicine will continue to rely heavily on collaborations with SMEs, underlining the need for funding and support mechanisms within the new framework.

For Alzheimer's disease, early diagnosis is critical. Currently, in Europe, products that combine treatments with diagnostics have no single pathway to authorisation. The treatment will be assessed by the EMA and often the diagnostic component by a national regulator.

The revision offers a chance to introduce a streamlined assessment pathway, enabling a single scientific advice process for these products. And that makes a real difference when developing innovative treatments for complex diseases like Alzheimer's.

The revision is a pivotal moment for the EU pharmaceutical sector. Get it wrong and we will continue to lose ground to the US and China. But get it right and we can help Europeans live longer and feel better, all while driving the EU's resilience and economic growth.

Julie Spony, Policy Officer, EPF

The last few months have been crucial for the patient community as the European Union (EU) undertakes a major overhaul of its pharmaceutical legislation, 20 years after it was first adopted. This complex but critical revision will have an impact across the EU on the development, authorisation and access to medicines, which are key aspects of treatment for patients with chronic conditions.

This revision offers a once-in-a-generation opportunity to create a more patient-centred EU regulatory framework by promoting patient involvement in the regulatory process, improving access to safe, effective and high-quality medicines, and developing new medicines that better address unmet patient needs. While the European Commission's initial proposals already included measures to improve patient access to medicines, the European Parliament's negotiating position, adopted a few months later, takes us even closer to this goal. It strengthens patient involvement, particularly in managing shortages and within the European Medicines Agency, and improves the information available to patients about their medicines.

However, more needs to be done to truly prioritise patients' needs. This includes incorporating patient experience data into the evaluation of medicines and maintaining a strong focus on enhancing access to medicines. The coming months will be equally crucial as the Council of the EU finalises its official negotiating position and inter-institutional negotiations begin. These discussions must continue to promote a patient-centred approach and ensure that the new rules benefit those they affect first and foremost: the patients.

Promoting pan-European clinical research: the European Alzheimer's Disease Consortium

The European Alzheimer's Disease Consortium (EADC), which was established in 2001, is a network of research centres of excellence in Europe. Registered as a non-profit association and scientific society, the EADC currently includes 60 specialist centres and memory clinics, spread across 20 countries in Europe, as well as several associate members.

1. **BELGIUM:** Antwerp - Leuven - Liege - Louvain-Brussels
2. **BULGARIA:** Sofia
3. **CROATIA:** Zagreb
4. **CZECH REPUBLIC:** Prague - Brno
5. **DENMARK:** Copenhagen
6. **FINLAND:** Kuopio
7. **FRANCE:** Bordeaux-Lille-Marseille-Montpellier-Nice-Paris-Paris-Toulouse-Tours
8. **GERMANY:** Berlin-Bonn-Cologne-Erlangen-Goettingen-Leipzig-Mannheim-Munich-Ulm
9. **GREECE:** Thessaloniki-Athens
10. **ITALY:** Brescia-Genoa-Milan/Monza-Perugia-Roma-Siena
11. **NETHERLANDS:** Amsterdam-Maastricht-Nijmegen-Utrecht
12. **NORWAY:** Stavanger
13. **PORTUGAL:** Lisbon-Coimbra
14. **ROMANIA:** Bucharest (2)
15. **SERBIA:** Belgrade
16. **SLOVENIA:** Ljubljana
17. **SPAIN:** Barcelona (3)-Madrid
18. **SWEDEN:** Malmo-Stockholm/Huddinge
19. **SWITZERLAND:** Bern-Geneva-St Gallen
20. **UNITED KINGDOM:** Bath-Bristol-Edinburgh-London (2)

Figure 8: Map showing EADC members

The EADC aims to stimulate pan-European scientific research on Alzheimer's disease (AD) and related dementias, including clinical trials and other research projects. By fostering collaboration and promoting exchange between organisations and clinical experts, the EADC advances research and supports the development of improved diagnostics, interventions and treatments. In the last two decades, since it was founded, EADC members have collaborated on several EU-funded research projects, as well as many global clinical trials of treatments for AD and other dementias.

The EADC holds biannual meetings, providing a forum for scientific exchanges between members, discussions on industry developments, and updates on EADC activities. The association also publishes position papers, review articles, clinical guidelines and consensus statements developed through collaborative engagement with EADC members. Recent publications include position statements on anti-amyloid therapies and diagnostic disclosure, and harmonised protocols for analysing Positron emission tomography (PET) and Magnetic Resonance Imaging (MRI) scans. For more information about the EADC, visit: https://eadc.online/

Acknowledgements and References

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