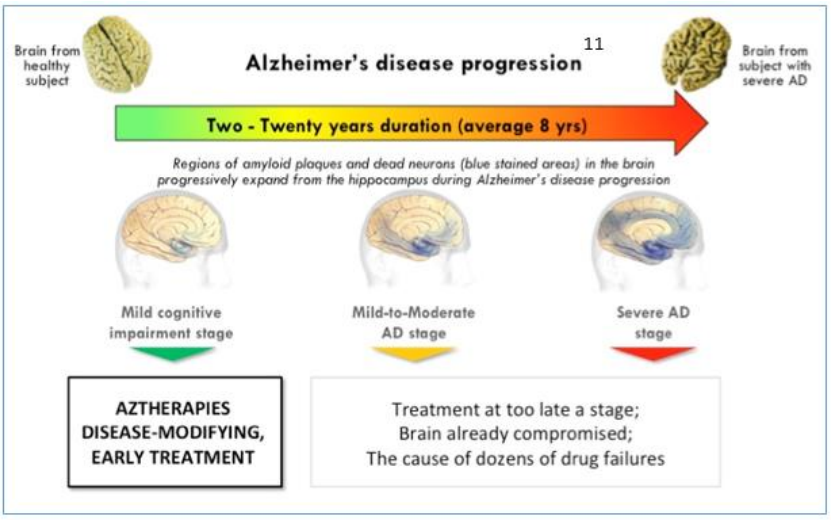
Project Management

Context

The global prevalence of dementia has been estimated to be as high as 24 million, and is expected to reach over 100 million by 2050 as average life expectancy increases.[1] There are over 9.9 million new cases of dementia diagnosed each year worldwide, implying one new case every 3.2 seconds.[2] Alzheimer's disease (AD) is the leading cause of dementia globally, affecting 60-65% percent of people with dementia, and approximately seven million people in Europe.[3] AD is a neurodegenerative disease that slowly and progressively destroys brain cells. Features of this disease include formation of amyloid plaques (*a sticky build-up of a protein that is normally found throughout the body*) and tangles in the brain (*where the structural fibres begin to twist and tangle)*. AD affects memory and cognitive function, which may lead to confusion, changes of mood and disorientation.[4]



Alzheimer's disease places a huge burden on families, carers and health systems. The total annual cost of Alzheimer's disease is estimated at €515 billion, similar to the annual gross domestic product (GDP) of Belgium.[5] In 2001, France became the first European country to launch a national dementia programme. By February 2008, President Sarkozy pledged €1.6 billion to this initiative.[6] This was the prototype used by the G8 Global Dementia Summit in December 2013, under the leadership of UK Prime Minister David Cameron and US President Barack Obama which committed to address the epidemic of AD through increased collaborative research, innovation and partnerships, with the stated ultimate aim to "cure AD by 2025".[7]

Current AD treatments only provide minimal, short-term symptomatic relief; none slow disease progression and there is no cure. Research through clinical trials can take decades to complete. Currently there are only five European Medicines Agency (EMA) and Food and Drug Administration (FDA)-approved medicines to treat Alzheimer's disease.[8] There is widespread consensus on the continuing urgent need for additional research, increasingly focusing on ways to prevent the onset of Alzheimer's disease in the first place, as it is now well known that signs of Alzheimer's disease can be found in the brain decades before the first symptoms appear in the patient.[9-11] This need for innovative, fast and effective research is, however, severely hampered by:

- The difficulty of identifying people who are likely to develop Alzheimer's dementia (it is estimated that 80-90% of candidate patients are not eligible for clinical trials)[12]
- Our poor understanding of the earliest stages of the disease
- Lack of flexibility in the way clinical trials are typically performed
- Pharmaceutical development organisations conducting trials in isolation to maintain competitive advantage

The last novel AD treatment was approved by regulatory agencies in 2004, and the success rate in AD clinical trials since then has been 0.4 percent.[13,14] These trials have cost hundreds of millions of dollars[15] in addition to the inherent emotional and human costs associated with the disease.

European Prevention of Alzheimer's Dementia (EPAD) is a public–private consortium, funded by the Innovative Medicines Initiative (IMI) and several pharmaceutical companies, designed to increase the likelihood of successful development of new treatments for the prevention of Alzheimer's dementia.[16]

EPAD
European Prevention of Alzheimer's Dementia Consortium

In **traditional clinical trials**, half of the research participants may receive the potential new medicine, and half may receive placebo (*a dummy medication with no active ingredient*). For reasons of competition between pharmaceutical companies, each clinical trial is designed and conducted independently of those being performed with other potential medicines. This results in inherent inefficiencies, for example in terms of the large number of research participants already exposed to a placebo arm that could potentially be reduced if, given the right infrastructure, data were shared between studies.

Adaptive design clinical trials are those where the design is modified based on ongoing assessment of data. They can avoid large numbers of research participants potentially being exposed to doses of experimental medicines that could have been identified as ineffective earlier in the study, and allow for more promising treatments to be prioritised in a dynamic way. Adaptive design in clinical trials has proven to be hugely successful in development of potential treatments in other therapeutic areas such as breast cancer,[17] and offers great promise in the development of novel treatments for Alzheimer's disease.

EPAD will help with the development and testing of potential new medicines in the pre-dementia population through four main strategies:

- Development of the EPAD Registry of approximately 24,000 research participants, who may be at increased risk of developing Alzheimer's disease, using data from other existing local/national registries
- Establishing an EPAD Longitudinal Cohort Study (LCS) of 6000 people at any one time, selected from the Registry, that allows follow-up of people over time and observation of development of any Alzheimer's disease symptoms
- Establishing an adaptive, proof-of-concept (PoC) trial that includes 1500 participants at any given time drawn from the LCS, for dynamically testing promising new therapies or combinations of medicines
- Use of the data obtained through EPAD to improve understanding of the disease and its underlying mechanisms, through advanced modelling approaches

People

EPAD is a large consortium consisting of 38 partnering organisations including academic institutions, pharmaceutical companies, small and medium-sized enterprises (SMEs), Contract Research Organisations (CRO) and vendors from across Europe.[16] Reflecting the significance of Alzheimer's disease, this consortium includes several organisations that are natural competitors, but who have come together to collaborate in a pre-competitive setting. The innovative nature of the project also means that most organisations in EPAD need to move beyond their 'comfort zone' and challenge well-established practices in pursuit of the ultimate goal. The political significance of the EPAD vision was demonstrated in the General Assembly meeting held in Stockholm, May 2017, where Queen Silvia of Sweden joined over 150 delegates from participating organisations, funding agencies and other stakeholders in attendance.[1]

Due to the large and complex nature of the work and the multiple stakeholders, EPAD is managed as a programme. The Work Breakdown Structure was based on a total of eight different work packages (WP), where each team has different roles and responsibilities according to expertise and track record. Each WP, covering one of the large functional areas, was further broken down into sequential tasks and sub-tasks allowing for milestone and deliverable definition and monitoring.[1] To facilitate appropriate interfacing, two clusters were identified within the programme: a Delivery Cluster (including WPs related to scientific reasoning, modelling, EPAD Registry, LCS and PoC trial), and a Supporting Cluster (including WPs on project management, communication, sustainability, ethical, legal and social implications). Downstream, cross-cutting committees were established, most notably a Data Oversight Committee, and an Intellectual Property and Legal Committee, providing a supplementary layer to the programme's governance structure, each with participation of several WP members. Upstream, decision-making was enabled by the set-up of an Executive Committee (ExCom) overseeing all WPs, assisted by a Clinical Development Executive in charge of monitoring the work on the two critical components of the programme, the LCS and PoC trial platforms, and a Project Management Office (PMO).

This complex organisation required a multi-faceted, yet efficient project management structure, with special emphasis on the key LCS project. EPAD selected QuintilesIMS as the Contract Research Organisation to project manage the EPAD LCS, complemented by Synapse Research on programme management duties leading the PMO, which included representation of the leading pharmaceutical company (Janssen) and the Project Coordinator and study sponsor (University of Edinburgh). Immediately on award, QuintilesIMS appointed a Project Manager (PM) to act as the primary contact for the project sponsor team from the University of Edinburgh. The PM also leads a team of Clinical Research Associates (CRAs; who act as the primary interface with the participating Trial Delivery Centres (TDC)), Data Managers and support functions necessary to deliver the EPAD LCS to the agreed scope and schedule. Under the supervision of the PM, the CRAs provide training and local support to the participating Trial Delivery Centres during the set-up and conduct phases of the project. Programme budget management and cost monitoring is a responsibility of the PMO, a task more complex than usual due to the cost-sharing philosophy of the IMI funding scheme, and the relative inflexibility of pre-agreed commitments of participating pharmaceutical companies. Special care has to be taken that trade-offs are not solved at the expense of quality or time.

Six main Trial Delivery Centres in the UK, France, Spain, Sweden, Netherlands and Switzerland were initially identified to participate at the start of the project.[18] Setting up these centres was the milestone signalling completion of phase 1 of the project. Becoming National Leads, these core centres are then essential in expanding the project to other TDCs within their respective countries. With the magnitude of this ambitious EPAD initiative, additional TDCs are being identified and added to the project on an ongoing basis. As these new TDCs have been identified, QuintilesIMS has pro-actively added additional team members with expertise in expediting project start up, and procedures have been dynamically added at the programme level to deal with new situations, and to create the adequate incentives.

As LCS sponsor, University of Edinburgh appointed their own team to oversee the research coordinators and consultants, as well as act as the global liaison between the partnering pharmaceutical companies, third party vendors and QuintilesIMS. Through the use of web-based technologies, extensive cross-functional team meetings, and continual ad hoc discussion, the level of ownership and collaboration has evolved what otherwise would be three distinctive teams – QuintilesIMS, Synapse and University of Edinburgh – into one successful, high performing project team. This level of team work has been a key success factor in the advancement of the EPAD LCS project.

Key tasks managed by this interdisciplinary management team include:

- Set-up and training of TDC site staff
- Management of discussions with ethics committees and regulatory authorities, necessary to obtain the legally required approvals for the project to commence
- Supporting participating TDCs with training on the project protocol (*the regulatory document which determines how the project will be administered, what its objectives are, and how success will be measured*), as well as providing clarification on medical and other logistical questions
- Monitoring, collection and cleaning of the project data generated
- Integration of data from multiple vendor sources into an innovative EPAD data sharing platform
- Budgeting and cost monitoring for central services and TDCs, embedded into global programme budget management
- Change control to make sure that appropriate flexibility is in place to adapt to the many local, regional and national specifics affecting this project, in particular regarding costings and specific regulations/governance pertaining to the different institutions involved. This aspect was particularly important to secure engagement in the context of an 'open' collaboration framework

Combined across University of Edinburgh, Synapse, QuintilesIMS, the pharmaceutical companies, multiple vendors and TDC staff (including physicians, nurses, and support staff) approximately 400-500 team members are actively involved in the conduct of the EPAD LCS project. With such a large and diverse group of project stakeholders, focused and targeted communication, clear goals and objectives, and defined roles and responsibilities have been essential. Effective cross-functional coordination across the multiple stakeholders, drives positivity and efficiency of team dynamics, with internal recognition awards such as those employed by QuintilesIMS, used to maintain motivation and reward excellent performance. Specific workflows and guidelines were produced to provide clarity among project participants on the procedures and milestones of this project.

Delivery

QuintilesIMS took the decision to assign a PM and primary support team from their Edinburgh office, to facilitate close communication with the project sponsor, University of Edinburgh. Such close proximity has enabled frequent and cost-effective face to face meetings, to reinforce focus on project objectives, as well as to review progress against the projected delivery schedule. The project team feel that this personal face to face approach has promoted a greater team spirit, increased productivity and driven a tight focus on project delivery. Additionally, the PMO chairs bi-weekly teleconferences with relevant stakeholders.

A web based SharePoint site is used to facilitate communication across the project management team, TDC staff, third party vendors and EPAD PMO. This provides consistent messaging, status and progress vs plan information for all stakeholders. Synapse provided a proprietary 'dashboard-like' IT tool (*Synapse PI*) for the EPAD programme facilitating updates to the ExCom on project progress, including key metrics, via 'snapshot' views on the most important project aspects (top risks, deliverable status, twitter-like highlights, etc.). This allows evidence-based decision making, so that the sheer size of the project does not lead to confusion and disconnect between what happens on the ground and the highest authority in the project's governance structure.

Data from research participants are recorded in a web-based Electronic Data Capture (EDC) system, provisioned by a third party vendor and managed by QuintilesIMS. The Data Management team at QuintilesIMS worked collaboratively with the team at the University of Edinburgh, during the design phase of the EDC system to make sure that the structure and content coincide with the protocol-mandated data collection requirements. QuintlesIMS provides ongoing user training and support for primary users at the participating TDCs. Centralised and consistent data capture provides the relevant EPAD committees with real time access to project data, driving actionable insights and pro-active decision making.

Each participating TDC has a dedicated and named Clinical Research Associate assigned by QuintilesIMS, who acts as their primary contact and assures both the quality of the data collected and the timeliness of delivery. CRAs establish a personal relationship with the staff, visiting the site several times a year. Assignment of CRAs to TDCs is performed in a geographical manner, which in Europe is particularly important to facilitate communication in the local language.

The LCS project is progressing well, meeting the target of all six primary TDCs open before the end of June 2017 (completion of project phase 1), with research participants enrolling at a steady rate. The data being generated on the project are of good quality, which is testament to the training and monitoring provided. The adaptive design of the EPAD LCS allows the team to react quickly to study needs, balancing the available pool and providing the right candidates for the various treatment arms in the follow-on Proof of Concept study. This adaptive nature also means that the project scope evolves. Updates to scope are managed using a robust integrated change control process, which involves joint clarification of new roles and responsibilities and full change order management. When relevant, these changes are reviewed upstream at the programme level, where the master workplan for the whole of EPAD is maintained and updates are contractually formalised with the funding agency.

What makes the EPAD LCS different to other clinical trials is that participants are pre-selected from existing registries and cohorts using innovative solutions that enable the fine-tuning or 'balancing' of the LCS cohort composition. The

Register was engineered and project managed to act as research participant discovery system, called PREPAD (Participant Register for EPAD),[1] that draws ethically safe data from existing cohorts to pre-select participants. Specific workflows and tools have been built around a "Balancing Committee"[1] that has real-time access to PREPAD and LCS data to visualise 'cohort telemetry', which is used to accelerate or slow down recruitment from the different sources as needed. Participants are identified and followed up with no planned project end date, meaning this is a highly dynamic process, in which people will leave and enter the LCS continuously, but the cohort needs to remain fit for purpose. It is anticipated that this will yield a screen failure rate for the PoC trial much lower than in traditional clinical trials. Looking ahead, an important enabler to continuing project success will be management of the risk posed by staff turnover, to maintain project team continuity. Good project documentation and robust transition planning will be essential to mitigating the risk of loss of 'tribal knowledge' and project history due to such personnel changes. Most of all, maintenance of the culture and values created within EPAD as a space for open collaboration that transcends the naturally competitive environment in the market (among pharmaceutical companies, TDCs, and even different project management companies) will be critical in achieving long term success.

Innovation

An important success factor for the entire EPAD programme, and more specifically for the Proof of Concept clinical trial, is the flexibility to adapt the project design based on observed participant outcomes. For example, following ongoing data analysis, if it is evident there is need for more cognitive testing data at a certain time point, the protocol can be reactively adapted to include extra assessments within each treatment arm. This dynamism and adaptive nature has been embedded into every project component. While this has presented challenges, it is the unique factor that will allow EPAD to make a difference.

The EPAD LCS project protocol mandates several complex clinical procedures and assessments that may be outside the usual standard of care for the research participants. These include numerous tightly scheduled brain imaging measurements through Magnetic Resonance Imaging (MRI), as well as lumbar punctures and genetic testing. Consistent delivery across the TDCs is assured via robust pre-qualification assessment of site capabilities, as well as comprehensive training delivered by the dedicated CRAs. Together with regular and focused data monitoring, this provides sufficient confidence in the quality of the data to determine whether further design changes are required, to meet the ongoing needs of the diverse set of stakeholders. EPAD has also set-up a Participants Panel with representatives from the Trial Delivery Centres, which enables the project to respond to the views of the research participants in the design and implementation of clinical trials.

The results from the genetic testing and spinal fluid analysis, which could indicate presence of a genetic mutation and an increased likelihood for developing early onset AD, have to be managed sensitively, confidentially and in compliance with applicable country-specific disclosure requirements. Full support both to participants and their families is offered throughout the study, with the agreed approach fully endorsed and approved by Ethics Committees prior to use. The Balancing Committee also uses these data to make sure that the LCS population is representative of the full range of risk profiles across the Alzheimer's disease population.

Global reporting tools such as the QuintilesIMS' Infosario® platform (providing a comprehensive suite of visualisations and expanding access to current data on a wide array of project management areas, including site start-up progress vs. plan, milestones at risk, protocol deviations and data query volume) are being used by the QuintilesIMS project management team to drive continuing compliance with agreed schedule and quality commitments, and form the basis for reporting to stakeholders on status and progress vs. plan. This is coordinated with programme-level planning and risk management, and project progress assessment via 'objective' (Earned Value-based) approaches combined with 'subjective' stakeholder perceptions ('wisdom of the crowd' approaches), to estimate degree of completion of the project.

Within the QuintilesIMS project management team, formalised, holistic and integrated Stage Gate Reviews (SGRs) seek to optimise engagement of key internal stakeholders at pivotal points in the project lifecycle, to improve up-front delivery strategy, plan development prior to study start-up, and execution according to plans during conduct. These SGRs establish a formal structured review and oversight process, and have become an inherent part of the project culture, leading to a more transparent environment where project teams and stakeholders have the right conversations at the right times. This drives remediation of potential roadblocks, challenges assumptions, and proactively identifies and mitigates risk before they can escalate into issues, improving predictability and reducing surprise for stakeholders.

Results, Short-term and Long-term Project Benefits

Challenges Overcome

The key to good project management is making time to plan effectively at the beginning of the project, underpinned by early, robust, comprehensive and iterative risk management. The output of the planning process is the integrated project management plan (IPMP), which governs how the project will be executed, monitored, and controlled. Key components of the IPMP developed for this project include establishing the performance measurement baseline, a schedule of key milestones, clearly and unambiguously defined roles and responsibilities, and a thorough risk registry that identifies and weighs potential risks at every stage of the project and includes mitigation plans to overcome them. The most important challenge faced by EPAD was derived from its very nature as a complex, non-hierarchical, public-private partnership; which limits how traditional PM practices can be applied.

To counter this, three pillars are continuously enforced: 1) creating and socialising a shared vision; 2) establishing positive work dynamics across stakeholders; and 3) implementing tailored communication strategies. Key to this, is the environment of 'friendly' peer-pressure which creates buy-in from all stakeholders into the dynamic and adaptive project strategy. Incentive creation was a priority, e.g. the creation of the EPAD Academy to boost career opportunities of younger team members and create fair data access mechanisms that maximise academic output.[1] This all required a delicate PM balance that offered flexibility in some procedures without sacrificing (and to, actually, preserve) the core project elements.

The consistency in project management approach and team employed for the LCS and Proof of Concept trials has facilitated data sharing, as well as providing valuable run-in data for participants enrolling in the latter.

Every clinical trial presents its own project-specific risks, including those related to safety, operational and management aspects. By doing this work up front, and also thanks to the collaborative spirit and experience sharing across partners, the project team has been able to successfully leverage lessons learned from previous projects to avoid or mitigate the impact of these common problems. Research participant enrolment risks, for example, are often linked to the prevalence, complexity and severity of the disease, and the EPAD LCS project is no different. Identification and enrolment of Alzheimer's disease participants is exacerbated, as they may currently have no clearly visible physical symptoms and once diagnosed, patients require very specialised care.

The EPAD programme has been designed to mitigate the issues seen in traditional model clinical trials, particularly in the identification of potential participants. With the Registry as a pre-enrolment step, eligibility assessment and screen failure rates for future trials such as the EPAD Proof of Concept study (demonstrating clinical efficacy of potential new medicines in the treatment of AD) should be very much reduced. Running multiple potential treatment arms in parallel has the further advantage of allowing real time comparison of relative efficacy.

The EPAD initiative is further reducing the high risk of participant ineligibility, by using known sources of participants who are at increased risk of developing AD, and measuring disease progression with a combination of physiological and biochemical assessments. Trial Delivery Centres are selected upon meeting robust qualification criteria, one of which is that they must have access to an already existing local register of potential participants, which feeds the Registry. Standardising the protocol-mandated assessments to obtain a homogenous data set, while managing participants within the appropriate standards of care for their country, and making sure that participation in this project causes minimal disruption to their day-to-day lives, is critical to success.

As well as compliance with appropriate country-specific standards of care and regulatory requirements, negotiation of language and cultural challenges in the management of participants is very important. The local support provided to the TDCs by the assigned Clinical Research Associates has been a key factor in the success seen in this area. A significant challenge has been maintaining the balance between the need to meet demanding project timelines and managing team morale. Regular and transparent communication, together with a reward system for innovative and exemplary individual and team performance, have been very effective in maintaining team motivation.

Strictly from the project management organisation's point of view, the staggering complexity of the EPAD programme demanded the participation of several management teams, and specialised attention to the LCS project as core workplan component. Carefully designed governance mechanisms and coordination across levels makes sure that high and low-level workplans are aligned, that focus is kept on delivery, and that stakeholders are appropriately informed for timely decision-making. Creating a culture of open collaboration and a space for pre-competitive research, in which the project itself was seen as "adaptive" to evolving requirements, was challenging in the early stages but ultimately a critical success factor in delivering to plan and within budget.

> This project has numerous advantages over current approaches. These include the excellent pre-trial characterisation of research participants to inform selection and reduce screen failure, the establishment of the highest possible quality study sites across Europe, the rapid decision making on the likely success of a drug (or combination of drugs) in subsequent confirmatory trials as well as access to a shared placebo group.
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> Serge Van der Geyten
> *EPAD Coordinator and Director for Neuroscience External Affairs at Janssen Pharmaceutica NV*

Short-term Benefits

The EPAD LCS project is designed to provide long term monitoring of both the general health, and any Alzheimer's disease progression indicators in up to 6000 research participants at any one time. It is expected that completion of the primary project outcome measures will occur by end of 2019.[18] This is a novel way of approaching Alzheimer's disease, and although the short term benefits may not be immediately apparent to the individual research participants, they may receive early access to potential new preventative treatments by agreeing to participate in the follow on Proof Of Concept study.[16] The Participants Panel[1] assures that communications to participants are focused and directed to demonstrate the value of their engagement with QuintilesIMS in this project.

The EPAD LCS project has recently reached an important milestone with all six of the primary Trial Delivery Centres now open and actively enrolling research participants. This was a challenging outcome that was completed on schedule, and has been a greatly celebrated milestone within the EPAD community.[16]

> Preventing the development of dementia in biomarker-positive people would be a fantastic step forward in our fight against Alzheimer's disease. The EPAD and its novel trial concept will hopefully help speed up the drug discovery progress and bring us closer to this ambitious aim.
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> Jean Georges
> *Executive Director of Alzheimer Europe*

Approximately 240 participants have already been successfully enrolled on the project and collection of data is ongoing.[1] Data for this study are transferred monthly, and constantly monitored by the Balancing Committee. This approach drives 'real time' monitoring of the characteristics of the enrolled research participants, allowing much more targeted identification and assignment of patients to the appropriate treatment arm in the follow on Proof of Concept trial.

Long-term Benefits

The EPAD LCS project aim is to increase the understanding of the biological changes seen in Alzheimer's disease progression over several years, even before symptoms may be evident. Some of the early research participants are now in their 2nd year of the cohort study. On completion of the project, it is expected that the following assessments will have been completed:

- > 100,000 laboratory samples collected
- > 10,000 brain scans
- > 12,000 cognitive assessments
- > 12,000 clinical assessments

This large body of data will be made available for analysis to help researchers everywhere improve their understanding of the early, pre-dementia phase of Alzheimer's disease.[16]

Ultimately, the hope is that this project will reinvigorate the development of preventative treatments for one of the most challenging diseases facing our ageing society, one that affects 225,000 people who develop dementia each year in the UK alone.[19]

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