Brainteaser

D10.10
Exploitation Plan (M24)

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EXECUTIVE SUMMARY

Wherever we look in the healthcare industry, we can find new technologies being used to fight illness, develop new therapies and medical products, and help people live healthier lives. This is also the case of BRAINTEASER, a data science project that seeks to exploit the value of big data, including those related to health, lifestyle habits, and environment, to support patients with amyotrophic lateral sclerosis and multiple sclerosis and their clinicians.

Exploitation is a crucial activity of BRAINTEASER as it connects the results of the project to their subsequent market commercialization, aiming to a broader reach to patients and their families, physicians and caregivers, healthcare professionals and clinical societies, pharmaceutical and health monitoring companies, insurers, and other stakeholders involved.

Task 10.5 – Exploitation Plan focuses on the development of a business framework for the commercialization of software and tools delivered by BRAINTEASER to maximize their sustainability and socioeconomic impact. The outcome of the task is an exploitation plan, whose preliminary version (represented by this deliverable) is released at M24. An updated version including feasible exploitation routes will be discussed during a dedicated Exploitation Workshop at M42. The final version of the Exploitation Plan will be released as deliverable D10.11 at the end of the project at M48.

This first version of the Exploitation Plan contains a description of the solutions developed so far within the project and potential business contexts-of-use, in terms of technical features and indication of target users; followed by a through market analysis focusing on Amyotrophic Lateral Sclerosis and Multiple Sclerosis diseases, Medical Simulation solutions, and Wearable Healthcare Technology; and finally a preliminary exploitation strategy including a business model canvas, sustainability plans, and aspects concerning certification and Intellectual Property Rights protection.

The current plan represents the preliminary exploitation strategy envisaged for the project, and it will be updated during the project's lifecycle to reflect the evolution and the developments in the project outcomes. This document is intended to stimulate, encourage, and facilitate project partners' efforts in the exploitation activities of the main findings and outputs arising from the applications to be developed.

1 INTRODUCTION

Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) are chronic diseases that cause progressive or alternating neurological function deterioration (motor, sensory, visual, cognitive). Patients must balance care at home and hospital stays on an as-needed basis, dealing with ongoing uncertainty about when the condition may become acute, as well as a significant psychological and financial burden that extends to their caregivers. On the other hand, clinicians require tools that can assist them throughout all stages of patient care, provide tailored treatment options, and flag urgently required treatments.

Modeling and Simulation (M&S) and Artificial Intelligence (AI) represent a key opportunity to successfully meet these needs, including: i) better describing disease mechanisms; ii) stratifying patients according to their phenotype assessed throughout the disease evolution; iii) predicting disease progression in a probabilistic, time-dependent manner; iv) looking into the impact of the environment; and v) suggesting interventions that can slow the progression of the disease.

With the help of low-cost sensors and apps, BRAINTEASER brings together unique personal and environmental data with big clinical datasets. Agile and user-centered design principles are used to create software and mobile apps that consider the social, psychological, and technical requirements of the target audience. BRAINTEASER is creating a system able to ensure patient data protection and ownership in order to provide quantitative evidence of the benefits and effectiveness of utilizing AI in healthcare pathways by establishing a proof-of-concept of its usage in a real-world clinical setting.

Exploitation is a crucial activity as it connects the results of the project to their subsequent market commercialization, targeting a broader reach to patients and their families, physicians and caregivers, healthcare professionals and clinical societies, pharmaceutical and health monitoring companies, insurers, and other stakeholders involved. In this deliverable, a preliminary definition of the exploitation strategy for the BRAINTEASER project's results is presented, comprising the following elements:

1. Description of the marketable results of the BRAINTEASER project, with their envisioned context-of-use and value proposition, business model and target users.
2. Through market analysis focusing on ALS and MS diseases, Medical Simulation solutions, and Wearable Health Technology, covering industry overview, current and future market size, growth rate and competition landscape.
3. Preliminary exploitation strategy including a business model canvas, sustainability after project end, pricing scheme, certification aspects and Intellectual Property Rights (IPR) protection and management.

2 AI IN HEALTHCARE

Healthcare is one of the most critical sectors in the broader landscape of big data because of its fundamental role in a productive society. AI in healthcare is an umbrella term used to describe the application of machine learning (ML) algorithms and other cognitive technologies in medical settings; it analyzes and acts on medical data, from molecular and genetics testing to medical imaging, usually with the goal of predicting a particular outcome.

Using patient data and other information, AI can help doctors, nurses, and other healthcare workers in their daily work by making healthcare more predictive and proactive. Big data analysis allows us to develop improved preventive care recommendations for patients, produce more accurate diagnoses and treatment plans, lead to better patient outcomes overall and enhance quality of life. AI can also predict and track the spread of infectious diseases by analyzing data from government, healthcare, and other sources. As a result, AI can play a crucial role in global public health as a tool for combatting epidemics and pandemics.

2.1 AI tools in disease progression

Advances in AI, patient-level "big data," and cutting-edge analytics are now helping companies better engage patients and their Healthcare Providers (HCPs) by understanding a patient's status, disease progression, and treatment journey. AI can reveal leverageable patterns and interactions that would otherwise go unnoticed, empowering pharma brands with a better, more efficient approach in an ever-escalating competitive environment. Finally, AI can be leveraged to tackle the increasingly complex challenge of intricate pathways to disease progression for niche patient populations.

There are multiple considerations that impact disease progression. Certain clinical decisions can or must be made quickly, while others can be prolonged over time when HCPs and patients take a "watch and wait" approach. Disease progression considerations and related clinical decisions can include comorbidities, patient age, and treatment response.

Readily identifiable population level patterns could suggest disease progression, but the journey can be intricate and unique to a given patient or subgroup. AI can meet the needs of these complex situations, as it powers tools that can close targeting and engagement gaps, driven by patient-level therapy transition predictions.

AI can be used to predict disease progression and related clinical events at many key points in the patient journey, including:

- First line treatment initiation
- Later line treatment transition
- Initiation of a target medication (specific brand)
- Initiation of a broad group of related medications (i.e., similar or the same drug mechanism of action or therapeutic target)

AI is not bound or limited by data complexity. It thrives on it. From patient specific factors to HCP-driven variables, AI models can quickly consider all available information to make accurate predictions so pharma marketers can act with confidence. Interactions, sequences, and timing can all be accounted for, providing predictions driven by a holistic view of the patient and their HCP(s).

Identifying patients ready to start or transition treatments is meaningful. However, not knowing when those patients are ready can limit the impact of engagement. AI could help solve this, too, with timed-based assessments. Models can be trained to predict start and transition events in advance and to make these predictions a set amount of time before the event.

Innovations in digital disease tracking technology may allow for the accumulation of real-world (RW) patient data in real time that can be integrated into burgeoning machine learning databases. Advances in data collection technology, such as developments in biosensors and disease tracking remote applications for smartphones, unlock access to an unprecedented wealth of disease data. Using AI technology to sift through and derive meaningful patient care implications will be essential to capitalizing on these novel databases.

Moreover, such new AI tools could help designing make clinical trials more efficient and effective using a strategy called predictive enrichment. The basic idea is that, for any medicine, some people are more likely to benefit than others — so if a trial only enrolls likely responders, the study will need fewer participants to detect a statistically meaningful effect.

2.2 Challenges for AI in healthcare

As indicated in a recently published review[1], despite the growing evidence on the benefits of AI in healthcare and the great advances and the high level of maturity of AI in certain clinical domains, its application remains limited and is used most often only in laboratories and testing and is still scarce in clinical practice, limiting the measure of its impact in people's health.

There are challenges to adopting AI in healthcare, including having to meet regulatory requirements and overcoming trust issues with machine learning results, where doctors do not understand how the system works, healthcare workers hesitate in accepting AI results, and patients are reluctant. Moreover, methodological aspects should be duly considered to make real progress in benefitting science and, therefore, universal health care, including a better understanding of the information selected by AI algorithms, appropriate multicenter and longitudinal validations of results and practical aspects regarding hardware and software integration.

During the BRAINTEASER development, dedicated tasks will work on thorough testing on the data collection infrastructure, accuracy of AI prediction, and to the definition of

[1] https://doi.org/10.1016/j.ijmedinf.2022.104855

clinical guidelines, recommendation for public health authorities and certification roadmap. The goal is to increase the expected favorable reception and acceptance by end-users, where doctors and patients are properly educated, and misconceptions are eliminated.

3 BRAINTEASER OUTPUT DESCRIPTION

3.1 Exploitable Results and Paths

Exploitable results can be divided into marketable and non-marketable, including all outcomes of the project with commercial and non-commercial exploitation potential mainly in the EU and US markets.

Exploitable results can be summarized as follows:

- Professional and patients' tools and technologies (marketable)
  - Patient app
  - Clinical tools
  - Community of Practice
- AI Models (marketable):
  - Disease monitoring and short-term risk alert
  - Patients' stratification
  - Disease progression
  - Personal exposure to pollutants
- Data and project results (non-marketable)
  - Clinical data
  - Sensor data
  - Environmental data
  - Open challenges

This preliminary exploitation plan will focus on the marketable results, for which a detailed description is provided in the following paragraphs.

3.1.1 Professional and patients' tools and technologies

The main output of WP3, led by partner UPM, is the design and development of solutions for patients, health professional and stakeholders in ALS and MS. WP3 has 3 relevant outputs, the mobile app used by patients, the tools for clinicians and the Community of Practice.

3.1.1.1 Patient App

The BRAINTEASER Patient App is a digital intervention mobile application deployed on both Android and iOS platforms, that allows to self-assess the health status and daily activities of the individuals through the completion of validated questionnaires, and to report the symptoms suffered including details that allow the clinician to anticipate some decisions about treatments or interventions related to the progression of the disease. It also supports the reception of personalized care through educational content, rehabilitation exercises, mindfulness, and cognitive games. With the Patient App it is also possible to contact the health professional and get in contact with patient associations in

the area. The app also integrates two wearable sensors that track the user's daily physical activity, sleep quality, heart rate, respiratory rate, and the exposure to pollutants. All data collected is presented in the Clinical Tool.

3.1.1.2 Clinical Tool

The Clinical tool is a dashboard in a web format for healthcare professionals, either nurses or neurologists, who monitor the patients. The clinical tool is used to remotely follow-up the evolution of ALS and MS patients and provide the appropriate tailored support to patients according to their specific needs. With this tool, professionals will be able to access the data reported by the patients, while using the Patient App, regarding the responses to the questionnaires, the symptoms, and the activity of the intervention modules through educational content, mindfulness practices, or cognitive games. A module presenting the results of the AI models will also be available for the doctor to visualize the prediction of the disease progression to adjust earlier the treatments and the kind of support for patients and caregivers. These tools will also support the modification of personalized digital therapies that are included in the patient's application to maintain a state of general well-being and alleviate the detrimental physical and mental effects of the disease.

3.1.1.3 Community of Practice

The BRAINTEASER Community of Practice is a collaborative space for clinicians, experts by experience, caregivers, and the general public with interest in the use of artificial intelligence and other digital tools for the management of ALS and MS diseases. This space has been designed as a virtual Community of Practice embedded in the project's website, and is comprised of several sections: General knowledge inputs to amplify the information regarding the use of digital tools and personalized medicine approaches in the management of ALS and MS diseases; personal stories recorded from patients, researchers and physicians; public activities such as fundraising initiatives; clinical advices specifically recommended by experts to help maintaining quality of life, and finally a contact form to allow direct conversations, requests and to foster collaborations outside the BRAINTEASER Consortium. The BRAINTEASER's CoP is the result of the efforts of the BRAINTEASER project to bring new knowledge and produce a comprehensive toolkit of resources and content of interest, available to everyone.

3.1.2 AI Models

3.1.2.1 Disease monitoring and short-term risk alert

The main output of WP5, led by partner UNITO, are AI-based models of continuum patient monitoring and AI-based alert system for early detection of adverse events. These models are designed to track patient progression and predict risk of adverse events using data entered by the clinician in the clinical tool, from the patient in the app, and from Garmin wearable sensors. A more detailed description will be provided in deliverable D5.2 to be released at M24, and in the upcoming scientific publications.

The envisioned context-of-use for these results is to provide clinicians with continuous progression tracking and early warning of adverse events for patients instead of relying only on periodic visits every few months. The clinician will be able to monitor the

progression/stage of the disease as predicted by the model and receive warnings about the predicted risk of adverse events. The input required by the models are the data collected from the patient through the BRAINTEASER app (including wearable sensors data), and data collected from the clinician through the clinical tool.

WP5 results started at M1 with Technology Readiness Level[2] (TRL) 1, represented by a set of already existing methods to be applied to BRAINTEASER prospective data (when available), in order to be tested for an initial selection. At M24, the initial implementation of the results reached TRL 2, but not enough data is available yet for a proper model, training and testing. Finally, it is expected that the functional models implemented in Python will reach TRL 4 at M48, with an assessment of the data quality and representativity, and of the AI models performance and limitations.

Compared to the state-of-the-art methods currently available in literature, progression tracking in nowadays clinical practice is based on questionnaires filled during visits, while BRAINTEASER models will leverage data coming from more frequent questionnaires done through the app and continuous sensor data.

The expected impact of WP5 solutions is to provide continuous tracking of patient progression and early alerts of possible adverse events. This may represent a very useful feature for healthcare centers and clinicians with less expertise with the specific disease.

The current limitations affecting the models is their dependance on data coming from apps, sensors and clinical tools, requiring the BRAINTEASER collection infrastructure to continue working after the end of the project in order to allow for commercial exploitation of the tools.

3.1.2.2 Patients' stratification

The main output of WP6, led by partner FC.ID, are AI-based models of patients' stratification. These models are designed to identify patient profiles and disease progression patterns. A more detailed description will be provided in deliverable D6.2 to be released at M24, and in the upcoming scientific publications.

The envisioned context-of-use for these results is to support clinical decision leveraging the identification of disease progression patterns and patients' profiles. Given data of a new patient, the clinician will be able to compare it with the output of the stratification models learned from other patients, in order to obtain a putative profile and disease progression pattern.

WP6 results started at M1 with TRL 2, due to the scarceness of AI stratification models, with poor validation for ALS and MS diseases, available in the literature. At M24, the initial implementation of the results reached TRL 4 with preliminary models having been implemented, while the outputs are currently being analyzed. Finally, it is expected that the models implemented will reach TRL 7 at M48, when the outputs will be fully

[2] Technology Readiness Level description as provided by the European Union: https://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf

analyzed, and further validation with prospective data by clinicians in clinical settings will be performed.

Compared to the state-of-the-art methods currently available in literature (as documented in deliverable D6.1), the stratification models currently in development will better describe the disease progression patterns and clinical and demographic characterization of the patients' profiles.

The expected impact of WP6 solutions is to provide clinicians with a better understanding of the disease and its progression based on the patient profile. This has a potential impact on clinical decisions regarding patient care and patient selection for clinical trials.

The current limitations affecting the models are that further validation is needed with prospective data in clinical settings, in particular the relationship between the AI models results and the clinicians with respect to disease diagnosis and thus therapeutic development in the long run.

3.1.2.3 Disease progression

The main output of WP7, led by partner UNITO, are AI-based Models for ALS and MS disease progression, predicting the whole patient progression with or without wearable sensor data. A more detailed description of the models will be contained in deliverable D7.2 to be released at M24 and in the relative scientific publication, while the validation and implementation details will be included in deliverable 7.3 to be released at M36.

The envisioned context-of-use for these solutions is to provide clinicians with explainable predictions about disease progression and possibly help in clinical decision making, for instance regarding treatments or other interventions. The clinicians will be able to run the models to obtain predictions about disease progression and adverse events. The model input could include sensor data or just routine clinical and environmental data that is widely available in most clinical settings.

WP7 results started at M1 with TRL 2, represented by the various predictive models scouted in scientific literature. At M24, the implemented models have reached TRL 3, and are currently undergoing testing and refinement on BRAINTEASER retrospective datasets. Finally,, it is expected that the functional models implemented in Python or R will reach TRL 4 at M48, with an assessment of their performance and limitations.

Compared to the state-of-the-art solutions currently available in literature (a list of such predictive models is presented in deliverable D7.1), BRAINTEASER models will leverage better training data with respect to many public datasets, focusing on explainability and inclusion of environmental data.

The expected impact of WP7 solutions is to provide clinicians access to useful predictive models that can facilitate clinical decisions. This may represent a very useful feature at HCPs for clinicians with less expertise with the specific disease.

The potential limitation affecting these models is their potential dependency on the data from wearable sensors and could thus be dependent on the persistency of BRAINTEASER data collection platform after the end of the project.

3.1.2.4 Personal exposure to pollutants

The main output of WP8, led by partner UNIPV, is an AI-based framework to compute personal exposure to pollutants at different spatial and temporal granularities. Personal exposure can be computed according to specific use cases that consider patients' status and rely on heterogenous data sources. A more detailed description of the models and their implementation can be found in deliverables D8.1 released at M12, and D8.2. released at M18.

The envisioned context-of-use for these results is the monitoring of the exposure to main air pollutants during everyday activity indoor and outdoor, leveraging the integration of information regarding personal exposure into AI-based models to better understand diseases progression and increase models' performances.

WP8 results started at M1 with TRL 2, with a sensor grid installed at the project partner site in Pavia. At M24, the developed results reached TRL 4, with the definition of a data acquisition pipeline and a proof of concept for the personal exposure computation. Finally, it is expected the personal exposure computation to be integrated in the AI models and applications will reach TRL8 at M48.

Compared to the state-of-the-art currently available in literature and on the market (for example pollution exposure monitoring using commercial air quality sensors and the Google Labs: Air Quality[3]), BRAINTEASER solution provides a finer granularity, and use cases that can be exploited in the context of disease progression monitoring.

The expected impact of WP7 solutions is to support clinical decision regarding lifestyle suggestions, and to encourage novel policies regarding air quality.

The potential limitation affecting these models are represented by the validation of models' accuracy, and their utility to be demonstrated when integrated into clinical tools.

3.2 Tools' usage, applicability and end-users

Each solution has a specific application, which results in specific target product lifecycle phase, mode of use and target users. Below, all these aspects are described in tables where each solution shows its peculiarities.

[3] https://insights.sustainability.google/labs/airquality

Solution applies to the following Product Area	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Healthcare Treatment	X	X	X	X	X	X	
Pharmaceutical	X	X	X	X	X	X	
Medical Devices	X	X	X				
Advanced Therapeutical Medicinal Product			X				
Environmental Monitoring			X				X

Solution applies to the following Product Lifecycle Phase	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Discovery			X		X		X
Design		X	X		X	X	
Preclinical	X	X	X				
Clinical	X	X	X	X		X	X
Manufacturing							
Post-Launch							

Solution applies to the following Product Lifecycle Phase	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Development / Optimization			X		X		X
Performance evaluation			X				
Safety Evaluation			X				
SiMD[4]	X	X	X	X	X	X	
SaMD[5]	X	X	X	X	X	X	

[4] Software in a Medical Device (software which helps in any way to run a medical device)

[5] Software as a Medical Device (software in its own right)

Solution can support	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Scientific Research		X	X		X		X
Clinical Research	X	X	X	X	X	X	X
Product Development	X	X	X				
Regulatory Approval			X				
Medical Training		X	X	X			
Clinical Decision Making	X	X		X	X	X	X

Targeted end-user	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Researcher		X	X		X		X
Clinician		X	X	X	X	X	X
Industry			X				
Regulators and Policymakers			X				
Patients	X		X				X
Public			X				X

Expected Market Sector	Patient App	Clinical Tool	Community of Practice	Disease monitoring	Patients' stratification	Disease progression	Personal exposure
Healthcare Providers HCPs	X	X	X	X	X	X	X
Public stakeholders monitoring tools							X

4 ALS DISEASE - MARKET ANALYSIS

ALS, also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that affects nerve cells in the central nervous system that control voluntary muscles. Muscle twitching, stiffness, and weakness due to a decrease in the size of muscles in the legs or arms are some of the common symptoms. Approximately half of people with ALS may lose their ability to swallow, breathe, speak, walk, and use their hands.

It is estimated that around 450.000 people worldwide are living with ALS[6], with over 50.000 people in Europe and 30,000 people in the United Stated suffering from the condition at any given time. The global number of patients with ALS is expected to rise by 69% between 2015 and 2040[7].

According to the National Institute of Neurological Disorders and Stroke (NINDS), following gradual paralysis, patients with ALS often die from respiratory failure within 3-5 years. It also states that between the two types of ALS, the sporadic type is the most common form, accounting for 90- 95% of all cases, while the remaining cases are inherited through a mutated gene, which is sono as familial type.

Although there is no cure for ALS, treatments such as medications and stem cell therapies can help manage symptoms, prevent complications, and slow the disease's progression. Adopting a sedentary lifestyle raises the risk of developing the disorder in the elderly, creating a need for novel therapeutic approaches and targeted treatment options. These factors are expected to drive the ALS treatment market even further[8].

4.1 Market Overview

The global ALS treatment market size was valued at USD 537.2 million in 2018 and is expected to grow at a compound annual growth rate (CAGR) of 5.8% from 2019 to 2026. Rising geriatric population, growing awareness about ALS, and increasing incidence rate are the factors driving this market. However, the high cost associated with ALS treatment may pose an impediment to the market during the forecast period[4].

4.1.1 COVID-19 Impact on ALS Market

As healthcare systems around the world have been severely disrupted in the aftermath of the coronavirus pandemic, COVID-19 had a significant impact on the ALS market as it affected not only diagnostic and treatment procedures but also research and development activities in the area. For instance, a survey by WHO conducted in 155 countries for three weeks in May 2020 has found that the COVID-19 pandemic has 'severely' disrupted the delivery of services to prevent and treat non-communicable

[6] https://als.eu/node/14

[7] Arthur KC, Calvo A, Price TR, et al. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun 2016;7:12408

[8] https://www.grandviewresearch.com/industry-analysis/amyotrophic-lateral-sclerosis-treatment-market

diseases (NCDs) in almost 80% of countries surveyed[9]. This showed that the prevention and treatment services of various chronic diseases, including various neurodegenerative disorders, had been severely disrupted, becoming a significant concern because people living with chronic disorders were at higher risk of severe COVID-19-related illness and death[10]. Additionally, a decline in clinical visits due to COVID-19 outbreak and lack of awareness among people will act as restrain and further impede the growth rate of the market during the forecasted period.

4.2 Market Dynamics and Opportunities

4.2.1 Surge in worldwide geriatric population

According to the United Nations World Population Prospects 2022 report[11], there are 77.1 million people aged 65 years or over living in the world in 2022, and this number is projected to reach 1.6 billion by the year 2050. This surge in the geriatric population is expected to increase the burden of rare neurological diseases which is likely to augment the growth of the studied market over the forecast period.

4.2.2 Increase in prevalence and incidence of the disease

According to the research article titled "Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis"[12] published in the Journal of Neurology in April 2020, the overall crude worldwide ALS prevalence and incidence were 4.42 per 100,000 population and 1.59 per 100,000 person-years, respectively. ALS prevalence and incidence increased by age until the age of 70-79. Hence, the rising prevalence of ALS diseases worldwide will likely trigger the demand for these drugs for treatment and thereby drive segment growth.

Furthermore, the article titled "Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and C9orf72 Genetic Variants"[13] published in Neuroepidemiology Journal in July 2021 stated that combined prevalence rates (per 100,000 people) and incidence rates (per 100,000 person-years) were 6.22 and 2.31 for Europe, 5.20 and 2.35 for North America, 3.41 and 1.25 for Latin America, 3.01 and 0.93 for Asian countries excluding Japan, and 7.96 and 1.76 for Japan, respectively. The increase in prevalence and incidence of the disease is expected to increase the demand for the treatment and thus boost the market growth.

4.2.3 Advancements and increasing product approvals

The advancements and increase of product approvals, along with partnerships and collaborations by key players are helping in the market growth. For instance, in June 2021,

[9] https://www.who.int/news/item/01-06-2020-covid-19-significantly-impacts-health-services-for-noncommunicable-diseases

[10] https://healthpolicy-watch.news/covid-19-severely-disrupted-treatment-of-chronic-diseases-who-warns/

[11] https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf

[12] https://pubmed.ncbi.nlm.nih.gov/31797084/

[13] https://pubmed.ncbi.nlm.nih.gov/34247168/

CRISPR Therapeutics and Capsida Biotherapeutics Inc. entered into a strategic partnership to research, develop, manufacture and commercialize in vivo gene editing therapies using CRISPR technology delivered with engineered AAV vectors for the treatment of familial ALS and Friedreich's ataxia. Such partnerships are likely to bolster market growth[14].

Furthermore, the engagement of various companies in clinical trials and new drug development associated with ALS treatment will boost the growth of the market segment. For instance, in April 2020, GENUV, Inc. began the Phase 1 and 2 clinical trials to evaluate the safety, tolerability, and efficacy of trametinib (SNR1611) in the treatment of amyotrophic lateral sclerosis and is expected to be completed by December 2024[15].

4.3 Healthcare Costs

ALS is a rare disease that has a significant economic and social impact. According to a recent study, the annual total cost per patient ranged from US$ 13,667 in Denmark to US$ 69,475 in the United States[16].

Another study conducted in the United States discovered that monthly costs per patient increased 9 months before diagnosis, peaked at the index month (Medicare: US $10,398; commercial: US $9354), and then decreased but remained high post-index[17].

HPCs diagnosing and treating patients with ALS represent an important potential target sector for BRAINTEASER solutions and tools, since clinicians were the most frequently identified target end-user for their scientific and clinical research, clinical decision making and medical training.

4.4 Pharmaceutical Competitive Landscape

The ALS treatment market is slightly fragmented in nature due to the presence of several companies operating globally as well as regionally. Some of the major players in this competitive landscape are:

- ☐ Mitsubishi Tanabe Pharma Corporation
- ☐ Sun Pharmaceutical Industries Ltd
- ☐ CORESTEM, Inc
- ☐ BrainStorm Cell Limited
- ☐ Amylyx Pharmaceuticals Inc.
- ☐ AB Science
- ☐ Ionis Pharmaceuticals

[14] https://pharmanewsintel.com/news/crispr-therapeutics-capsida-collaborate-to-develop-gene-therapies

[15] https://clinicaltrials.gov/ct2/show/NCT04326283

[16] Gladman M, Zinman L. The economic impact of amyotrophic lateral sclerosis: a systematic review. Expert Rev Pharmacoecon Outcomes Res 2015;15:439–50.

[17] Meng L, Bian A, Jordan S, et al. Profile of medical care costs in patients with amyotrophic lateral sclerosis in the Medicare programme and under commercial insurance. Amyotroph Lateral Scler Frontotemporal Degener 2018;19:134–42.

- ☐ Biohaven Pharmaceutical
- ☐ Biogen
- ☐ F.Hoffmann-La Roche AG

As the first indication of market segment characteristics[18], a total of 156 companies working on ALS disease were identified, whose headquarters are located primarily in the Americas (83), followed by Europe (42) and Asia-Pacific (31).

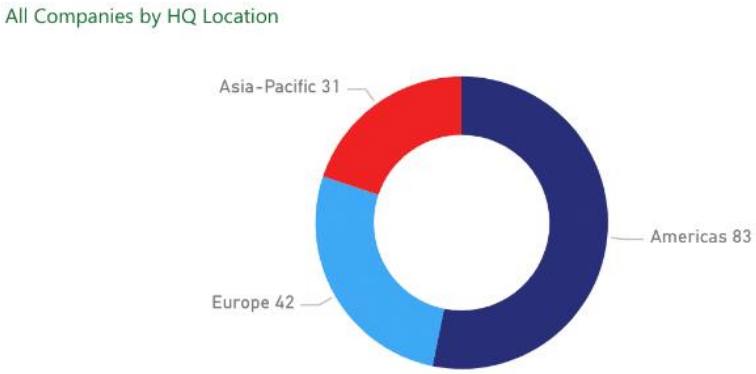

Figure 1 - Pharmaceutical Competitive Landscape for ALS – Worldwide distribution

Out of 156 total companies, 75 were identified as Private Biopharma, 72 as Public Biopharma and 8 as Other Organization.

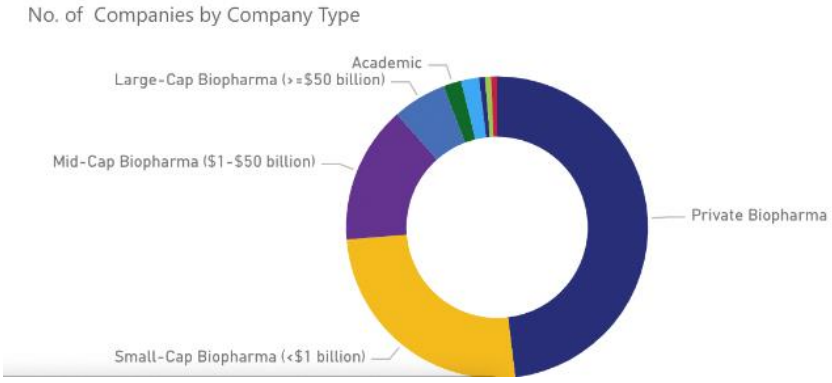

Figure 2 - Pharmaceutical Competitive Landscape for ALS – Company Types

[18] http://pharma.globaldata.com/

Among the Public BioPharma, 40 were identified as Small-Cap Biopharma (<$1 billion), 23 a Mid-Cap Biopharma ($1 - $50 billion,) and 9 as Large-Cap Biopharma (>=$50 billion).

Figure 3 - Pharmaceutical Competitive Landscape for ALS – Public Biopharma Companies by Market Cap Tier

39 companies have already a marketed product, while 167 products are currently on different phase of development: 29 in Research, 64 in Preclinical, 2 in Investigational New Drug application, 21 in Phase I, 4 in Phase I/II, 26 in Phase II, 1 in Phase II/III, 11 in Phase III, and 9 are in Registration/Approved/Market.

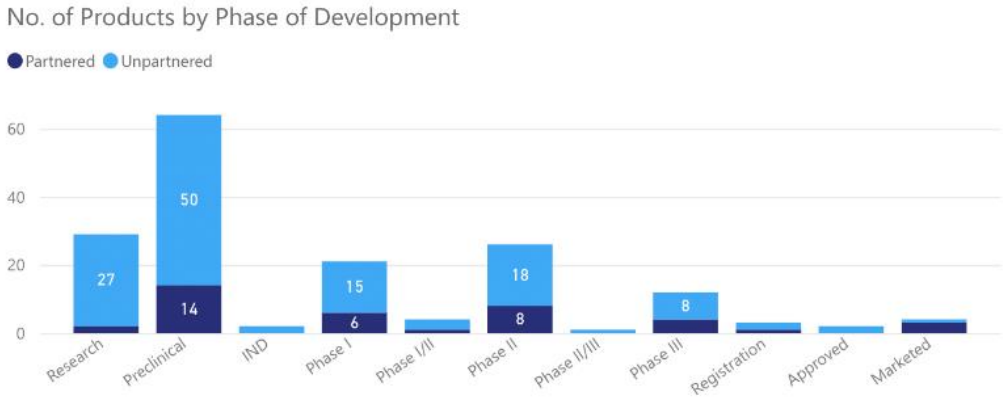

Figure 4 - Pharmaceutical Competitive Landscape for ALS – Products by Phase of Development

Pharmaceutical companies working on ALS products represent an important potential market sector for BRAINTEASER solutions and tools, since they could be used for stratification of patients and monitoring of patients during clinical studies, and to be offered to clinicians and practitioners as digital companion for their drug products.

5 MS DISEASE - MARKET ANALYSIS

MS is a chronic inflammatory immune-mediated disease that affects nerve cells in the spinal cord and brain, causing demyelination, axonal transection, and neurodegeneration. MS affects more than 700.000 people in Europe and 400.000 people in the United States and 2.5 million people globally. Each year, the number of people diagnosed with MS rises, necessitating the development of new medications that are more effective and have fewer side effects.

Injectable, oral, and infused medications, muscle relaxants, antidepressants, and physical therapy are some of the most widely utilized therapies. Interferon-beta and glatiramer acetate are injectable therapies that are given under the skin or into the muscle; oral medications include teriflunomide, dimethyl fumarate, and cladribine; and intravenous infusion treatments include ocrelizumab, alemtuzumab and natalizumab.

5.1 Market overview

MS market was valued at USD 25.32 billion in 2021 and is expected to reach USD 33.98 billion by 2029, registering a CAGR of 3.75% during the forecast period of 2022 to 2029. On the other hand, the high cost associated with the treatment of MS is expected to obstruct the growth rate of the market. The dearth of skilled professionals and lack of healthcare infrastructure in developing economies will challenge the MS market as well[19].

5.1.1 COVID-19 Impact on MS Market

Similarly, to the considerations of COVID19 Impact on ALS market described in paragraph 3.1.1, COVID may continue to have a negative impact on the market of MS in the next months. A decline in clinical visits due to COVID0-19 outbreak and lack of awareness among people will act as restrain and further impede the growth rate of market during the forecast period.

5.2 Market Dynamics and Opportunities

5.2.1 Increasing Prevalence of Multiple Sclerosis

The rising prevalence of MS is a primary driver of the market's growth. Relapsing-remitting multiple sclerosis (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS) and progressive-relapsing MS (PRMS) are the types of MS disease, and their high prevalence rate will influence the market dynamics during the forecast period[20].

[19] https://www.databridgemarketresearch.com/reports/global-multiple-sclerosis-market

[20] https://www.fortunebusinessinsights.com/industry-reports/multiple-sclerosis-drugs-market-100386

5.2.2 *Increasing Investment for Healthcare Infrastructure*

Another significant factor influencing the growth rate of MS market is the rising healthcare expenditure which helps in improving its infrastructure. Governments and non-government organizations in developed and developing countries are increasing their efforts to raise awareness of multiple sclerosis and giving significant funds for drug research and development. Furthermore, rising initiatives by public and private organizations to spread awareness will expand the MS market. Additionally, high disposable income and increase in the development of innovative monoclonal antibodies, immunosuppressants, immunomodulators and interferons will result in the expansion of MS market. Along with this, rising geriatric population and continuously changing lifestyle will enhance the growth rate of the market[16].

5.2.3 *Increase in the number of research and development activities*

The market's growth is fueled by an increase in the number of research and development activities. This will provide beneficial opportunities for the MS market growth. Along with this, rising drug approvals and launches will further propel the market's growth rate. Moreover, rising investment for the development of advanced technologies and increase in the number of emerging markets will further provide beneficial opportunities for the multiple sclerosis market growth during the forecast period[16].

5.3 Healthcare Costs

MS is a costly chronic disease, with prescription drug costs and indirect productivity loss being significant cost drivers. The International Multiple Sclerosis Study stated the average annual costs for each patient to be €41,212, with direct medical costs standing at €21,093, direct non-medical costs of €2110, and indirect costs to be €16,318[21]. A cross-sectional study from 16 European countries presented the total mean annual costs per patient with MS to be € 22,800 for mild disease, € 37,100 for moderate disease, and € 57,500 for severe MS[22].

According to a 2019 study[23], the total economic burden of MS in the United States was estimated to be $85.4 billion, with $63.3 billion in direct medical costs and $22.1 billion in indirect and nonmedical costs. The three largest components of direct costs were retail prescription medication (54%), clinic-administered drugs, medication, and administration (12%), and outpatient care (9%). The average excess per-person annual medical costs for patients with MS were $65,612; disease-modifying therapies (DMTs) accounted for the largest proportion of this cost, at $35,154 per person. The cost of DMT per user ranged from $57,202 to $92,719, depending on gender and age. The average indirect and nonmedical costs per patient with MS were $18,542 and $22,875 when caregiver costs were factored in. The largest indirect cost components were lost earnings due to premature death, presenteeism, and absenteeism losses.

[21] https://journals.sagepub.com/doi/10.1177/1352458517737388

[22] https://journals.sagepub.com/doi/10.1177/1352458517694432

[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9109149/

HPCs diagnosing and treating patients with MS represent an important potential market sector for BRAINTEASER solutions and tools, since clinicians were the most frequently identified target end-user for their scientific and clinical research, clinical decision making and medical training.

5.4 Pharmaceutical Competitive Landscape

The market for MS therapeutics is consolidated, as there are few players in this market. These companies are the big pharmaceutical companies focusing on pipeline drugs for multiple sclerosis. With rising R&D investments in the pharmaceutical industry, it is believed that more companies may enter the market studied in the future, and the competition may increase. Some of the major players operating in the MS market are:

- F. Hoffmann-La Roche Ltd. (Switzerland)
- Mylan N.V. (US)
- Teva Pharmaceutical Industries Ltd. (Jerusalem)
- Sanofi (France)
- Pfizer Inc. (US)
- GlaxoSmithKline plc (UK)
- Novartis AG (Switzerland)
- Bayer AG (Germany)
- Eli Lilly and Company (US)
- Merck & Co., Inc. (US)
- Allergan (Ireland)
- AstraZeneca (UK)
- AbbVie Inc. (US)
- Johnson & Johnson Private Limited (US)
- Cipla Inc. (US)
- Abbott (US)
- Merck KGaA (Germany)
- Actelion Pharmaceuticals Ltd (Switzerland)
- Opexa Therapeutics, Inc. (US)
- Bayer AG (Germany)

As the first indication of market segment characteristics[24], a total of 202 companies working on MS Disease were identified, whose headquarters are located primarily in the Americas (99), followed by Europe (68) and Asia-Pacific (34).

[24] http://pharma.globaldata.com/

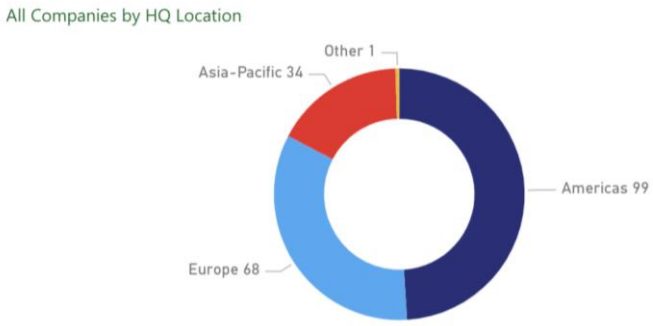

Figure 5 - Pharmaceutical Competitive Landscape for MS – Worldwide distribution

Out of 202 total companies, 92 were identified as Private Biopharma, 94 as Public Biopharma and 16 as Other Organization.

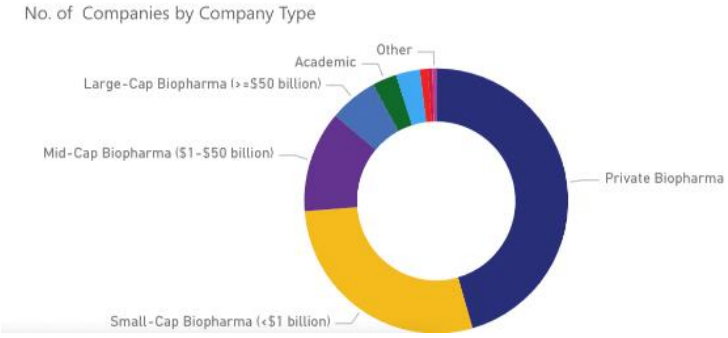

Figure 6 - Pharmaceutical Competitive Landscape for MS – Company Types

Among the Public BioPharma, 54 were identified as Small-Cap Biopharma (<$1 billion), 25 a Mid-Cap Biopharma ($1 - $50 billion,) and 12 as Large-Cap Biopharma (>=$50 billion).

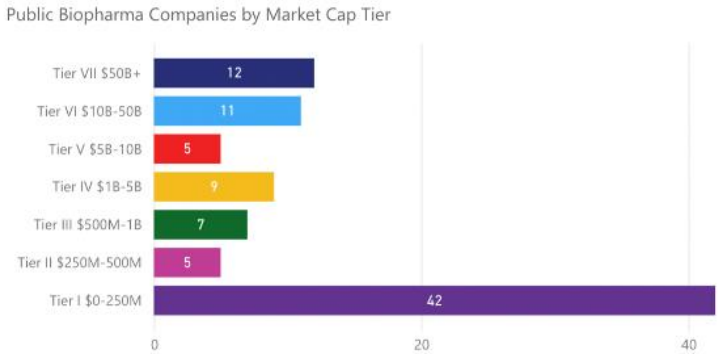

Figure 7 - Pharmaceutical Competitive Landscape for MS – Public Biopharma Companies by Market Cap Tier

64 companies have already a marketed product, while 215 products are currently on different phase of development: 18 in Research, 66 in Preclinical, 30 in Phase I, 3 in Phase I/II, 34 in Phase II, 2 in Phase II/III, 13 in Phase III, 3 in Registration, and 3 have been recently Approved.

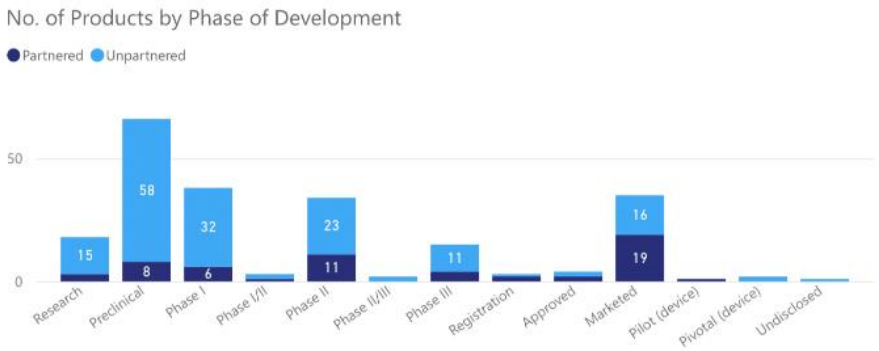

Figure 8 - Pharmaceutical Competitive Landscape for MS – Products by Phase of Development

Pharmaceutical companies working on MS products represent another Important potential market sector for BRAINTEASER solutions and tools, since these solutions could be used for stratification of patients and monitoring of patients during clinical studies, and to be offered to clinicians and practitioners as digital companion for their drug products.

Consortium member IST already offers on its web-based platform InSilicoTrials.com a tool dedicated to MS pathology, named MS TreatSim (Multiple Sclerosis Treatment Simulator - https://mstreat.insiliconeuro.com/), which allows for the creation of realistic virtual representations of patients with MS, based on a detailed mechanistic model of the underlying immune system and its dysregulation in MS, and to simulate Relapsing Remitting Multiple Sclerosis and its drug treatments. MS TreatSim is used by pharmaceutical companies working on MS products and may represent preferred access to potential target users interested in testing the BRAINTEASER solution.

6 MEDICAL SIMULATIONS - MARKET ANALYSIS

6.1 Industry Overview

Modeling and simulation (*in silico*) techniques allow to replicate and reproduce complex biomechanical and physiological processes, in order to support the development or regulatory evaluation of new medical products, devices or treatments. Through medical simulations, physicians, surgeons, medical professionals, and medical device producers have access to previously untapped knowledge that they may incorporate into product creation, diagnosis, and therapy for patients' benefit. Medical simulation encourages cross-domain ideas and ways to extend and sustainably improve existing processes or process chains; as a result, more and newer therapeutic options arise.

6.1.1 Digital Twin for Healthcare

Digital twins are digital representations of human physiology built on computer models, in which data relating to both the individual and the population are introduced. Technological advances are accelerating the creation of these digital twins, which underlie data-driven models capable of preventing, diagnosing, and treating diseases.

The use of digital twins in healthcare is revolutionizing clinical processes and hospital management by enhancing medical care with digital tracking and advancing the modelling of the human body. These tools may represent great help to researchers in studying diseases, new drugs and medical devices and may also help physicians optimize the performance of patient-specific treatment plans.

In the short term, digital twins will help the healthcare system in bringing life-saving innovations to market faster, at lower costs and with greater safety for the patient. The key to translating digital twins' value into real impact lies in large-scale implementation: making the technology widely accessible in the clinical routine, innovating key clinical processes using digital simulations, and improving medical care.

6.1.2 Translational Precision Medicine

Drug discovery and development now have unprecedented opportunities for new product and business model innovation, fundamentally altering the conventional approach to how drugs are discovered, developed, and marketed. This is especially true in the age of precision medicine, digital technologies, and artificial intelligence. Digital biomarkers, model-based data integration, artificial intelligence, biomarker-guided trial designs, and patient-centered companion diagnostics are important elements of translational precision medicine.

6.1.3 Data Science Platforms

A data science platform is a packaged software application that provides tools for the whole data science project life cycle. Data science platforms are essential tools for data scientists, allowing them to explore data, construct models, and distribute them. They make data processing and visualization easier while also providing a large-scale

computing infrastructure that facilitates user collaboration by providing a centralized platform. Because data science platforms have APIs that enable for model generation and testing with minimum outside technical needs, they function as a one-stop shop for data modeling[25].

The growing reliance on AI/ML demands the development of data science platforms capable of constructing, training, scaling, and deploying AI/ML-based models. Furthermore, AI/ML are propelling advancements in data science and data management, combined with increasing usage of cloud-based solutions and services. However, high investment costs, data privacy and security, as well as reliability issues, represent key obstacles

6.1.4 Healthcare simulation platforms

Digital platforms are transforming healthcare, with healthcare platforms set to become part of the 'new normal'. Medicine is evolving, and with the aid of in silico medical simulation, it has the potential to play a significant role in clinical practice.
Today healthcare simulation (platforms) can help companies reduce by up to 50% the time-consuming and costly development, as well as subsequent registration / certification processes of new drugs, medical devices and treatments. Though regulatory agencies are recommending companies to adopt these practices, many small and medium-sized biotech organizations may lack the IT infrastructure, expensive software, and high expertise needed to develop and use models.

6.2 Market Overview

The global AI in healthcare market size was valued at USD 10.4 billion in 2021 and is expected to expand at a compound annual growth rate (CAGR) of 38.4% from 2022 to 2030. The growing datasets of patient health-related digital information, increasing demand for personalized medicine, and the rising demand for reducing care expenses are some of the major driving forces of the market growth.[26]

In particular, the global medical simulation market size was estimated at USD 1.72 billion in 2020 and is expected to expand at a compound annual growth rate (CAGR) of 16.3% from 2021 to 2028. Growing technological advancements, preference for minimally invasive treatment, and focus on patient safety are the factors anticipated to boost the market growth. North America held the largest share of medical simulation in 2021 estimated to be around USD 900 million and is expected to expand at a compound annual growth rate (CAGR) of 15.8% from 2021 to 2028[27].

Based on products and services, the market is segmented into web-based simulators, healthcare anatomical models, simulation training services, and healthcare simulation software. The web-based simulation segment is expected to register the highest growth

[25] https://www.researchandmarkets.com/reports/5640491/global-data-science-platform-market-by-component

[26] https://www.grandviewresearch.com/industry-analysis/artificial-intelligence-ai-healthcare-market

[27] https://www.grandviewresearch.com/industry-analysis/simulation-software-market

to more than a quarter of the medical simulation market during the forecasted period (2021-2028) [22]. Factors responsible for the growth of this segment are the controlled and predictable learning environments and controlled access to simulation procedures.

6.3 Market Dynamics and Opportunities

6.3.1 Patient safety

According to a 2019 study published by the WHO[28], about 2.6 million people die every year in low- and middle-income countries due to patient harm in healthcare, making it the 14th leading cause of morbidity and mortality. Most detrimental errors are related to diagnosis and treatments. The rising number of medical errors and the need to ensure patient safety and high-quality care have become key priorities for healthcare organizations worldwide. Hospitals are expected to register the highest growth by end user of medical simulation market, with the increased focus on patient safety and the growing demand for minimally invasive surgeries being the factors attributed to the growth of this segment.

6.3.2 Growing geriatric population

The growing global geriatric population, changing lifestyles, rising prevalence of chronic diseases is expected to keep contributing to the surge in demand AI/ML technologies integrated into healthcare systems for early diagnosis, improved understanding and accurate prediction of diseases in their early stage based on historical health datasets progression in their initial stages[29].

6.3.3 Growing access to technologies

Growth in the medical simulation market can be attributed to factors such as growing access to technologies, well established distribution channels, digitalization of the healthcare force, rising number of upskilling healthcare professionals demanding hands-on patient training and the rise in demand for virtual and online training, as well as the presence of leading market players in the region.

6.3.4 Simulation-based training

The increased adoption of simulation-based training and certification of upskilling healthcare professionals could be an efficient means to improve patient safety and outcomes. This would result in a significantly larger addressable market than the current market, which is primarily education based. Training through simulation can help clinicians gain confidence knowledge and expertise for improving patient safety in a risk-free environment[30].

[28] https://www.who.int/news/item/13-09-2019-who-calls-for-urgent-action-to-reduce-patient-harm-in-healthcare

[29] https://www.grandviewresearch.com/industry-analysis/artificial-intelligence-ai-healthcare-market

[30] https://www.grandviewresearch.com/industry-analysis/medical-healthcare-simulation-market

6.3.5 Shortage in healthcare workforce

The growing shortage of healthcare workforce is expected to drive the adoption of AI/ML technologies to support care providers in quickly diagnosing the condition and devising an accurate treatment regime, reducing machine downtime, and minimizing care expenses. Owing to the Covid-19 pandemic, AI-based technologies witnessed a significant boost in adoption and are set to experience a dramatic growth trajectory[31].

6.4 Competititive landscape

Today, different digital twin solutions exist in healthcare to support industry and hospitals in the processes of development, planning, regulatory approval and post market surveillance of new treatments. Some of these platforms, like SimQ (simq.de), Novadiscovery's Jinko (www.novadiscovery. com/jinko) and Certara's Phoenix and Simcyp (www.certara.com/software), integrate models from partners or from literature, providing the user with an intuitive interface to setup, run models and visualize results.
Other solutions are not accessible by the user through web-based interfaces and require a higher level of expertise to the user, such as Elem (www.elem.bio), Sim4Life (zmt.swiss/sim4life) and other solvers like Comsol (www.comsol.com), Ansys (www.ansys.com) and Dassault Systèmes' products (www.3ds.com). Dassault Systèmes has also developed the web-based platform 3DExperience (www.3ds.com/3dexperience).

Partner IST has developed a cloud-based platform InSilicoTrials.com that provides a user-friendly computational modeling and simulation environment where many integrated, easy-to-use in silico tools are readily available. The platform primarily targets users from the medical device and pharmaceutical sectors. The in silico tools available for medical devices enable computational testing in different biomedical areas like radiology, orthopedics, and cardiovascular during product design, development and validation processes. For the pharmaceutical sector, the platform provides access to in silico tools developed at all stages of the drug discovery and development processes and for many different therapeutic areas. Our main differentiator from other market players are the models provided by academics, researchers, and regulators (such as the FDA).

6.5 AI/ML Enabled Medical Devices

As technology continues to advance every aspect of health care, software incorporating artificial intelligence (AI), and specifically the subset of AI known as machine learning (ML), has become an important part of an increasing number of medical devices. One of the greatest potential benefits of ML resides in its ability to create new and important insights from the vast amount of data generated during the delivery of health care every day.

Interest in medical devices incorporating ML functionality has increased in recent years. Over the past decade, the FDA has reviewed and authorized a growing number of devices legally marketed (via 510(k) clearance, granted De Novo request, or approved PMA) with ML across many different fields of medicine—and expects this trend to continue.

[31] https://www.grandviewresearch.com/industry-analysis/artificial-intelligence-ai-healthcare-market

FDA periodically releases an updated list of AI/ML-enabled medical devices marketed in the United States as a resource to the public about these devices and the FDA's work in this area. In October 2022, a total of 521 AI/ML-enabled Medical Devices were listed, distributed over several application areas:

- Radiology: 392
- Cardiovascular: 57
- Hematology: 15
- Neurology: 14
- Ophthalmic: 7
- Clinical Chemistry: 6
- General And Plastic Surgery: 5
- Microbiology: 5
- Anesthesiology: 4
- Gastroenterology-Urology: 6
- Pathology: 4
- General Hospital: 3
- Dental: 1
- Obstetrics And Gynecology : 1
- Orthopedic: 1

Only the 2.7% of AI/ML Enabled Medical Devices marketed In the United States addresses the Neurology Area, with applications ranging from computer-assisted recognition of EMG and EED patterns, to rapid assessment of traumatic brain Injury, automatic scoring of obstructive sleep apnea, diagnosis of autism spectrum syndrome, up to Image guided neurosurgery. The only device for continuous health monitoring Is the smartwatch EmbracePlus, marketed by Empatica. No marketed devices Is dedicated to ALS or MS pathologies.

7 WEARABLE HEALTHCARE TECHNOLOGY MARKET

7.1 Industry Overview

Wearable technology is any electronic device that is designed to be used while worn, often close to or on the surface of the skin, where they detect, analyze, and transmit information such as vital signs, and/or ambient data (such as keeping track of fitness level, steps walked, time spent exercising, calories burned …), and which allow in some cases immediate biofeedback to the wearer. Wearable technology has a variety of use cases which are growing as the technology is developed and the market expands, with products being categorized into wristwear, eyewear & headwear, footwear, neckwear, bodywear, and others.

Wearable devices in healthcare are designed to collect data of users' personal health and exercise (such as hearth rate, sleep monitoring, blood pressure, blood oxygen saturation, cholesterol levels, release of certain biochemicals…). These devices can even send a user's health information to a doctor or other healthcare professional in real time. The advancement of wearable technology and growing demand from consumers to take control of their own health has influenced the medical industry, including insurers, providers, and technology companies, to develop more wearable devices such as Fitbits, smartwatches, and wearable monitors.

Through digital health tech, doctors can connect with their patients via mobile applications and telehealth solutions. This allows doctors to monitor patients without visiting them in person. Advancements in Augmented Reality (AR) and Virtual Reality (VR) are gaining significant attraction in the healthcare segment. Moreover, VR technology is used in medical practice to assist in surgical training and procedures.

7.2 Market Overview

The global wearable technology market size was estimated at USD 52.14 billion in 2021 and is expected to reach USD 61.30 billion in 2022, and to grow at a compound annual growth rate of 14.9% from 2022 to 2030 to reach USD 186.14 billion by 2030. The wrist-wear product segment dominated the global industry in 2021 and accounted for the maximum share of more than 48.90% of the overall revenue, followed by eyewear & head-wear segment.

North America dominated the wearable technology market in 2021 and accounted for the maximum share of more than 34.20% of the overall revenue followed by the Asia Pacific and Europe regions. China is expected to be one of the most important countries in the Asia Pacific regional market owing to a rise in the number of vendors providing products with competitive features [32].

Piloted by the increasing demand of consumers to monitor their own health and keep track of their own vital signs, use of wearable technology has more than tripled in the last

[32] https://www.grandviewresearch.com/industry-analysis/wearable-technology-market

four years. The number of smart wearable users in US was estimated at 78.0 million (23.3% of population) and is expected to reach 93.7 million (27.2% of population) by 2025, with more than 80% of consumers willing to wear fitness technology[33].

7.3 Market Dynamics and Opportunities

7.3.1 Reliance on remote monitoring

Wearable technologies and ear-worn have witnessed robust growth as consumers rely on these devices for remote work, health tracking, fitness activities, and more. Rapid changes in consumer demographics, such as changing lifestyle patterns and preferences, are expected to boost product demand, which is anticipated to drive industry growth. In addition, high consumer spending on personal care products is projected to support the demand for wearable devices positively.

7.3.2 Increasing fitness awareness

The demand for smartwatches and fitness trackers among swimmers, cyclists, runners, and gym-goers is high as they provide fitness-related metrics and encourage a healthy lifestyle by providing information on calorie intake, water intervals, and step monitoring. In addition, many vendors are focused on introducing products with multiple sports options, a large display, a better battery, and a rugged metal casing attracting athletes. This is expected to drive the wearables technology market.

7.3.3 Increasing health awareness

Demand for wearables is projected to jump in the next few years as more consumers exhibit interest in sharing their wearable data with their providers and insurers. This growing demand for wearables has generated a booming market, and now insurers and companies are seeing how supplying wearable health technology to their consumers and employees is beneficial. Several manufacturers, such as Apple Inc., Garmin Ltd., Omron, and Nemaura, are focused on designing devices that provide information that includes clinical and non-clinical data. For instance, the sugarBEAT Wearable Technology by Nemaura allows frequent blood glucose monitoring in diabetic patients, eliminating the need for daily finger-prick calibration. Moreover, the use of wearable devices in healthcare due to the COVID-19 pandemic is rising as it offers several advantages and benefits to both patients and healthcare providers, which includes real-time health monitoring of vital statistics and earlier detection of disease or risk of a significant health event.

7.3.4 Improved data accuracy and regulatory clearance

As more consumers show interest in wellness wearables, they will have higher expectancy for device accuracy for healthcare purposes. However, in spite of the growing precision and wide variety of features of wearable technology currently on the market, the majority of them are not intended to serve a medical application. Some manufacturers, like Apple and Fitbit, have started seeking regulatory approval for specific features of their devices, such

[33] https://www.insiderintelligence.com/insights/wearable-technology-healthcare-medical-devices/

as ECG monitoring[34] and atrial fibrillation detection[35]. Following this path, healthcare solution company have started seeking regulatory approval for data collection solutions leveraging consumer wearable technology already available on the market[36], moving forward data-drive approach to care management, precision clinical care and improved clinical trial designs. Using wearable devices that have received regulatory clearance has significant advantages for consumers and patients related to data accuracy and privacy, ensuring that health data is treated with the same level of security of medical records.
In the next years, consumers trust is expected to increase toward high quality wearable devices with a regulatory clearance in terms of accuracy, reliability, and data quality

7.4 Competitive Landscape

Major manufacturers focus on new product launches to attain a competitive edge in the market and expand their product offerings. Some of the prominent players operating in the global wearable technology market include:

- ☐ Alphabet Inc.
- ☐ Samsung Electronics Co., Ltd.
- ☐ Sony Corporation
- ☐ Huawei Technologies Group Co., Ltd.
- ☐ Apple Inc.
- ☐ Xiaomi Corp.
- ☐ Adidas Ag
- ☐ Nike, Inc.
- ☐ Fitbit, Inc.
- ☐ Garmin Ltd.

Garmin wearable sensors were chosen by BRAINTEASER consortium for continuous monitoring tracking of patients involved in data collection. Garmin has expressed their interest in following the development of BRAINTEASER solutions in view of potential commercial partnerships at the end of the project.

[34] https://www.apple.com/healthcare/apple-watch/

[35] https://www.fitbit.com/global/us/technology/irregular-rhythm

[36] https://www.statnews.com/2022/06/13/apple-watch-parkinsons-rune-fda/

8 EXPLOITATION STRATEGY

8.1 Business Model

The main potential business model identified is Software-as-a-Service, offered through cloud-based platform infrastructure. Depending on the stage of automatization and scalability that will be reached at the end of the project, the commercial solution could require manual intervention offline in a first stage, to be then completely automatic in a next release (allowing the user to access a GUI that facilitates the data input process and the visualization of the results output). Partner IST was identified in the Grant Agreement as primary exploiter to license the solution for commercialization on the InSilicoTrials.com marketplace.

For a preliminary description of a business strategy for BRAINTEASER marketable results and their specific characteristics in terms of value creation and market orientation, we used the Business Model Canvas, one of the most well-known and relied-upon tools to help transform an idea into an organized strategy and an actionable business plan.

8.1.1 Business Model Canvas

The Business Model Canvas allows a wide snapshot of various aspects of the exploitation plan – everything from the value proposition and customer segments to operations and the financials. The tool itself, however, is no more complex than a series of nine boxes representing various commercialization strategy elements.

Using the business model canvas, we analyzed versatile aspects of potential commercial activity. However, the value proposition (VP) is its core, with all other units playing a supplementary role to the Value Proposition: left-hand units are mostly controllable elements managed by the consortium, while the right-hand ones are associated with the market and lie beyond our control.

In the business model canvas presented below we described the preliminary value proposition and key features and activities we intend to carry out to commercialize the project outputs, - to be further developed and specialized in next months

<table>
<tr><th colspan="5">BRAINTEASER Business Model Canvas</th></tr>
<tr>
<td rowspan="2">Key Partners

Key partners that will help our business model succeed will be all academic, clinical and industry partners involved during the project.
- ECHA and EBC multi-stakeholders connections
· Avicenna Alliance consortium and other international consortiums.
· External academic and scientific centers interested in assessing our solutions
· External clinicians interested in testing, giving feedback, or adopting our solutions
· Pharmaceutical companies interested in testing, giving feedback, or adopting our solutions
- Wearable sensors companies interested in testing, giving feedback, and integrating our solutions (e.g., GARMIN)</td>
<td>Key activities

- Dissemination and promotion at events, meetings, international conferences
- Sales&Marketing activities to offer value proposition, reach markets, maintain relationships with customer segments
- ·Refinement based on market feedback</td>
<td rowspan="2">Unique Value Proposition

The BRAINTEASER results will facilitate the monitoring and stratification of ALS and MS patients. through AI-based models.

- Integration of patient-generated data collected through low-cost wearable sensors and apps
- Dynamically modelling the entire disease progression over time
- User-centered design approach
- AI as a service business model
- Validation of a subset of models that support SaMD certification
- Open science paradigm to make solutions understandable to professionals and patients</td>
<td rowspan="2">Competitive advantage/ Innovative features

· Integrated and secure cloud-based platform able to standardize and bridge model simulations and in-silico trials.
· High-quality data expected to represent different communities and aiming to minimize bias in healthcare research.
· In-silico testing environment validated and positioned beyond the state-of-the-art in AI-based models developed by the academic partners in the project.
· Strengths of the consortium as scientific and technological experts
· Fluid exploitation strategy as “Software as a Service” (SaaS) of the developed in-silico trials through the project partner IST
· Feedback from open-evaluation challenges to experiment and compare different systems and solutions.</td>
<td>Customer Segments

· HCPs (clinical decision making and training)

- Pharmaceutical companies (stratification of patients during clinical studies)</td>
</tr>
<tr>
<td>Key Resources

· BRAINTEASER and InSilicoTrials brands, proprietary knowledge, intellectual property,
- Cloud-based infrastructure based on Microsoft Azure, management of allocated resources, solver licenses and potential agreements with solver vendors.
- IST’s experienced software developers, project managers and skilled sales force; consortium scientists, customer database</td>
<td>Channels

· IST sales force in EU and US and website
· Activities of communication and dissemination through the ECHA and EBC
· Consortium partners</td>
</tr>
<tr>
<td colspan="3">Cost Structure
The most important costs inherent in the business model are platform, cloud and license costs. In addition, we need to consider costs associated with the value of the models integrated within the platform, which will correspond to royalties provided to model developers. Finally, potential costs of training programs for end-users should be considered to avoid misconception and reluctancy.</td>
<td colspan="2">Revenue Structure
The Revenue Stream is generated by selling continuous access to the platform for a defined period of time. The fees will consist of different components: annual access, number of users, number of tools used, number of tokens (simulations to run).</td>
</tr>
</table>

8.1.2 Pricing scheme

The pricing scheme will take into account the cost structure and will use a value-based approach, i.e., a customer-focused strategy of setting prices primarily based on a client's perceived value of a product. Platform prices will include various options for the clients in order to meet their needs. The user will pay to access the platform on an annual basis, and then different prices will be available, based on:

- Use of a single tool or of more modelling and simulation tools available on the platform
- Number of simulations customers foresee to run, e.g., single simulation run, package of a certain number of simulations, annual fee with unlimited number of simulations, etc.
- Number of users accessing the platform under the same account, e.g., single users, small-medium collaborative teams, large corporate teams

8.1.3 Sustainability plan after the end of the project

Commercial agreements among partners will be defined by the end of the project to ensure the sustainability and socio-economic impact of the project after completion.

8.2 Certification

Every new product that enters the healthcare market needs to be cautiously developed first. In addition, if such a product may represent a hazard for human health, the product must undergo an extensive risk assessment, which in most countries and for most classes of hazardous products is regulated by law.

To achieve software certification, the software development performed during the project will need to be compliant to regulation and standards relevant to medical devices (i.e., UE Regulation 2017/745 and standards ISO 13485, ISO 14971, IEC 62304, IEC 62366), which guarantee that all user requirements received as input are specified, tested and validated in the final product.

During the BRAINTEASER development, procedural requirements are evaluated and utilized to enable future Software as a Medical Device certification, involving physicians and patients as stakeholders, and creating a set of recommendations for public health authorities. These aspects represent a very important asset in the definition of the value proposition of the solutions, increasing the expected favorable reception and acceptance by potential target-users (in particular for pharmaceutical companies) and eventually enhancing their appetibility. Depending on the stage of the regulatory qualification, the solution could be initially distributed for research use and pre-clinical use only. Task 1.4 “Defining clinical guidelines for AI models and software tools evaluation and collection of prospective data for SaMD certification” and Task 4.8 “Define and implement certification roadmap” are dedicated to this activity.

Moreover, the regulatory pathway for opinion and advice qualification will be evaluated. To provide a comparison, Total Kidney Volume (TKV) obtained through medical imaging

(such as MRI, CT or ultrasound) was formally qualified in 2015, both by FDA and EMA, as a prognostic enrichment biomarker for selecting patients at high risk for a progressive decline in renal function for inclusion in interventional clinical trials, hence for better identification of autosomal dominant polycystic kidney disease (ADPKD) patients. In the past years, several methods have been developed to make TKV assessment in ADPKD patients faster and more accurate, up to the most current methods based on completely automatic deep learning techniques developed by Mayo Clinic. Nowadays, these automated imaging and volumetric analysis for ADPKD are offered as service to both researchers and pharmaceutical clinical trials.

At M48, Deliverable D4.8 will contain detailed description of the certification roadmap and recommendation guidelines.

8.3 Intellectual Property Right and Management

Before the start of the project, the Partners have entered into a binding Consortium Agreement (CA) based on DESCA (Development of a Simplified Consortium Agreement), a comprehensive Model Consortium Agreement offering a reliable frame of reference for project consortia. Its scope is to ensure that each partner can exploit the results in an efficient, fair & equitable manner, to maximize the project impact. As it covers all aspects of administration, Partner relations & responsibilities, the CA also details the Access Rights to Foreground & Background and sets out availability rules for the participant Background needed for the project implementation, including possible limitations of use.

As a general principle, Access Rights for the implementation of the project are granted on a royalty-free basis, as the Access rights to Results will be for internal research activities. Access Rights to the Results needed for the exploitation of a party's own results shall be granted on fair and reasonable conditions, as will be the Access Rights to Background whenever similarly needed.

IP emerging from the project is mostly likely to include copyrights for software & algorithms, especially in WPs 3 to 8. The allocation of IPR in the Consortium will be based on the guiding principle in H2020, where Partners retain the ownership of their respective foreground. For joint efforts, there will be an up-front division of IP ownership among Partners according to core business areas & relative participations to the project deliverables, coupled with the default H2020 joint ownership whenever the respective efforts of the Partners cannot be ascertained directly.

The current IPR strategy will be upgraded during the project lifecycle, depending on outcomes' evolution. The above reflects the commitment made at the beginning of the project. As outcomes from the modelling and research activities become clearer, this section will be updated during the project lifecycle or at M48 at the latest

8.3.1 Horizon IP Scan

During the first half of 2022, partner IST applied and was accepted to participate to Horizon IP Scan[37], a tailored, free-of-charge, first-line IP support service provided by the European Commission specifically designed to help European start-ups and other SMEs involved in EU-funded collaborative research projects to efficiently manage and valorize IP in collaborative R&I efforts.

Horizon IP Scan entails three major steps:

1. a preparation phase including a pre-interview;
2. the main interview, which is done in an in-person or online meeting;
3. and the provision of a report and recommendations.

The service was delivered by the qualified IP expert SILVIA DONDI. During the main interview, a schematic summary was illustrated to IST for better understanding the management of IP within the Project. It was pointed out and remarked that the starting point for the co-operative BRAINTEASER project is sharing knowledge among the beneficiaries.

At the end of the service, the following main recommendations were provided:

1. Ensure the partners involved in the project takes the appropriate actions aimed at implementing a secrecy system regulating the treatment of all kinds of information, in particular labelling any confidential stuff exchanged with other parties as "confidential information".

2. Aim at protecting BRAINTEASER IP results (owned or co-owned), in particular:
   - Software by registering the copyright
   - Web interface by registering an industrial design or a copyright
   - Software/Data by creating a strong policy on secrecy measures
   In the case of joint ownership, negotiations shall be driven by the clauses set up in the CA.

3. Since dissemination is a goal of the Project, any conflicts with patentability purposes should be avoided. Dissemination of joint results shall be preceded by a notice given to the other co-owners at least 15 calendar days before publication, bearing in mind to carefully examine the material to be published and to raise any objection in due time.

4. Attention shall be drawn to implementing a policy on trade secrets and to deciding the best IP right on a case-by-case basis.

5. Freedom-To-Operate search on an international database is highly recommended for assessing whether the final products may be actuated is highly recommended. The FTO may also be updated later, before the launch on the market.

[37] https://intellectual-property-helpdesk.ec.europa.eu/horizon-ip-scan_en

8.4 Focus Group Webinars

A series of four Focus Group webinars is planned with the aim of enlarging the project's vision on users and market needs, obtaining additional requirements and accompanying the BRAINTEASER Consortium towards the most suitable results' sustainability and commercialization strategy.

Advocacy patient groups representatives, clinicians, policy makers, ICT professionals, ethical and standardization experts will be involved in a collaborative and participative discussion on clinical unmet needs, diseases course, clinical practice, new emerging research towards the development of more accurate and personalized treatment outcomes, to assess the BRAINTEASER approach and solutions and propose possible refinements.

By implementing the principles of participatory design, the experts will be engaged in a dialogue on clinical unmet needs, diseases course, clinical practices, new emerging research towards the development of more accurate and personalized treatment outcomes, to assess and enhance the BRAINTESER solutions and its exploitation approach.

The first webinar titled "Suitable Exploitation routes co-design" was organized on February 1, 2022, aimed at offering an overview of the BRAINTEASER project as a whole, spotting a light on the apps and clinical tools under development. The panel of speakers was composed of:

- Patient associations:
  - Pedro Carrascal - European Multiple Sclerosis Platform President
  - Patricia Jarabo Blázquez -Fundación Luzón
- Medical and scientific experts:
  - Andrea Caffo – EUPALS
- ICT experts:
  - Peter Wu - ASUSCloud CEO
- Policy Regulators:
  - Daniele Bollati – IMQ Product reviewer and Lead Auditor
- Ethical Experts:
  - Sofia Ortet - Nursing School of Coimbra,
  - Vojin Rakic - University of Belgrade · Center for the Study of Bioethics, European Division of the UNESCO Chair of Bioethics, Institute for Social Sciences, Belgrade
- Standardisation experts:
  - Catherine Chronaki - HL7 Europe Secretary General

The second webinar titles “How to maximize the use and value of healthcare data”, to be organized in January 2023, will provide an update on the ongoing BRAINTEASER activity, focusing on the great importance of quality data as fuel for AI-based solutions exploitation. Starting from what BRAINTEASER has already done and will do in terms of health data collection, data use and data sharing, the agenda of the webinar will tackle challenges and opportunities related to data quality. Which are the current obstacles? What about regulation, cost of anonymization, accountability and transparency? And are we fully taking advantage of the value of data sharing?