IDEA-FAST

Identifying Digital Endpoints to Assess FAtigue, Sleep and acTivities in daily living in Neurodegenerative disorders and Immune-mediated inflammatory diseases.

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List of Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AES	Apathy Evaluation Scale
AI	Artificial Intelligence
CoS	Clinical Observational Study
DIA-S	Depression in Old Age Scale
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FIS	Fatigue Impact Scale
FS	Feasibility Study
HD	Huntington's Disease
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
IBDQ-9	IBD Questionnaire-Short Form
IMID	Immune-mediated inflammatory disease
IoMT	Internet of Medical Things
ISCS	Inappropriate sleep composite score
MOS	Medical Outcomes Study
NDD	Neurodegenerative diseases
NHS	National Health System
OOP	Out of pocket
PD	Parkinson's' Disease
PDSS	Parkinson's disease sleep scale
PFS	Parkinson Fatigue Scale
PHI	Private Health Insurance
PROMISE F-SF	Patient Reported Outcome Measurement Information System Fatigue Short Form Questionnaire
PROs	Patient Reported Outcomes
PSQI	Pittsburgh Sleep Quality Index
PSS	Primary Sjögren's Syndrome
QoL	Quality of Life
RA	Rheumatoid Arthritis
RWD	Real world data
SHI	Statutory Health Insurance
SLE	Systemic Lupus Erythematosus
SSS	Stanford sleepiness scale
VAFS	Visual Analog Fatigue Scale
WP	Work Package

1 Abstract/Executive summary

The IDEA-FAST project aims to identify novel digital endpoints to assess fatigue and sleep disturbances in neurodegenerative disorders and immune-mediated inflammatory diseases. The project's initial investment will result in several exploitable assets that will aid key stakeholders to investigate fatigue and sleep disturbances and make use of the digital endpoints. To design an effective strategy for sustainability and exploitation, Work Package 9 aims to provide a thorough understanding of how various stakeholders can benefit from the proposed digital endpoints and ensure uptake of all other exploitable assets developed within the lifetime of the project. The present deliverable provides an initial framework for the socio-economic impact assessment and sets out the exploitation analysis framework. This work will contribute to ensuring that the exploitable assets generated within the project survive post-project funding and are consequently sustained.

2 Introduction

The IDEA-FAST project aims to identify novel digital endpoints to assess fatigue and sleep disturbances in neurodegenerative disorders (NDDs) and immune-mediated inflammatory diseases (IMIDs). The project's initial investment will result in several exploitable assets that will aid key stakeholders to investigate fatigue and sleep disturbances and make use of the digital endpoints. The work conducted in Work Package (WP) 9 will contribute to ensuring that the exploitable assets generated within the project survive post-project funding and are consequently sustained.

To design an effective strategy for sustainability and exploitation, WP9 aims to provide a thorough understanding of how various stakeholders can benefit from the proposed digital endpoints and ensure uptake of all other exploitable assets developed within the lifetime of the project. The present deliverable provides an initial framework for the socio-economic impact assessment and sets out the exploitation analysis framework. Overall, D9.2 contributes to the following WP9 objectives:

- Conduct a socio-economic impact assessment to gather the necessary evidence backing up the key benefits of implementing digital endpoints in clinical research and clinical practice.
- Identify and manage the intellectual property developed.
- Ensure optimal exploitation plans are drawn up, including an exploitation roadmap and specific business plan for commercialising the developed technology beyond the end of the project.
- Develop an effective strategy for sustainability.

Sustainability here refers to the maintenance and further development of key exploitable assets beyond the duration of the funding. Since the maintenance and development of assets imply certain costs, the sustainability plan will take into consideration appropriate business models to ensure income will be consistently generated in the long term, and at minimum, the corresponding costs are covered. Exploitation implies the use of the project's results at different levels, both during and after the implementation of the project [1]. These definitions are in line with the definitions put forward by the European Commission (EC), where sustainability is defined as follows: "A project is sustainable when it continues to deliver benefits to the project beneficiaries and/or other constituencies for an extended period after the Commission's financial assistance has been terminated"[2]. The EC further describes exploitation as "the utilisation of results in developing, creating and marketing a product or process, or in creating and providing a service, or in standardisation activities" [3].

The current deliverable provides the initial framework for sustainability and exploitation planning. A follow-up deliverable, D9.4, due at the end of the project, will report on the final state of exploitable assets and provide the results of sustainability and exploitation activities.

3 Methodology

To create an initial framework for the socio-economic impact assessment and sustainability and exploitation planning, several topics were investigated by desk research and expert interviews: how fatigue and sleep disturbances are conceptualised and managed, what are the current gaps in the delivery of treatment, and how digital endpoints can support this. Further, use cases for the use of the digital endpoints were defined, and based on these, stakeholders were mapped. To establish preliminary impact indicators for the identified stakeholders, costs associated with the two use cases were investigated: costs of clinical trials and related studies, as well as the socio-economic burden of fatigue and sleep disturbances in two health and care systems, namely Germany and England. As part of the exploitation and sustainability framework, user scenarios for the implementation of digital endpoints were created and shared with the consortium. An Exploitation and Impact Sub-committee was established as an expert group to oversee work on exploitation and sustainability within the project. With the help of consortium partners, a survey to identify key exploitable assets was performed and further described. Initial findings were presented across several consortium meetings with feedback used to stimulate further discussions with individual partners including expert interviews with health and care professionals as well as EFPIA partners. Finally, the framework delineated the steps needed for a defined sustainability strategy including further business modelling with a SWOT analysis, analysing public-private partnerships, integrating policy considerations and cataloguing challenges towards sustainability.

4 Definition of key concepts

4.1 Conceptualisation of fatigue and sleep disturbances

Fatigue and sleep disturbances are highly prevalent in many diseases, including NDDs and IMIDs. As symptoms, they are often debilitating, hard to conceptualise and measure, and lack specific treatment.

Fatigue is a multi-dimensional phenomenon including physical, cognitive, motivational, and emotional aspects. Experts report that currently, there is no scientific consensus or working definition of fatigue. It is highly variable and unpredictable, and several confounding factors are present. The most common features of fatigue associated with chronic diseases include the perception of fatigue as having no obvious 'explanation', a lack of improvement with rest, variability in severity, unpredictability and fatigue being profound or overwhelming.

Among dimensions of fatigue, physical fatigue can be expressed in people's inability to start, continue, or complete activities, as well as having a low level of energy. Despite sleep and rest, they do not always fully recharge their batteries. When patients feel fatigued, they report running on different percentages of energy. Furthermore, this can cause psychological turmoil, as patients do not understand the underlying cause of their symptoms. Mental fatigue also relates to the inability to fully recharge energy and often presents itself as the inability to concentrate or remember events and specific details. Patients' concentration is affected, and they often talk about a "mental fog". If it is not recognised as fatigue, it can create self-esteem issues, as they may perceive themselves flawed because they cannot function at the same speed or effectiveness.

As society already experiences fatigue and stress to a certain extent, a distinction needs to be made between fatigue, tiredness, and everyday tiredness. However, patients with chronic conditions report a much higher level of fatigue or tiredness than the general population.

Fatigue in immune-mediated inflammatory diseases, including Inflammatory Bowel Disease (IBD), is described as a sense of persistent tiredness, with periods of sudden and overwhelming lack of energy or feeling of exhaustion that is not relieved, or fully relieved following rest or sleep, resulting in a decreased capacity for physical and/or mental work. The importance of fatigue in patients with IBD has been increasingly recognised, with reported frequencies between 40% and 86% in patients with disease activity, and between 20% and 48% in patients in remission [4]. In addition, some studies have found that this symptom can affect the quality of life (QoL). In IBD, fatigue is the most frequent and disabling symptom when the disease is in remission. For this reason, suffering from fatigue is one of the main concerns of patients. Despite its clinical importance and the growing interest raised by health and care professionals in recent years, fatigue is poorly understood. The prevalence of fatigue in IBD patients is remarkably high and has a negative impact on QoL. Several factors are associated with fatigue in adults with IBD. The major contributors are disease activity, such as active inflammation, psychological stress, anxiety, and depression, and IBD medications [5].

Moreover, fatigue is present in other IMIDs, as in a UK-wide survey, fatigue was the most common reported symptom among Systemic Lupus Erythematosus (SLE) patients [6] and affects up to approximately 70% of Rheumatoid Arthritis (RA) patients [7].

Fatigue is also highly prevalent and poorly understood in NDDs. A study from 2018 discovered that 27% of patients with Parkinson's Disease (PD) reported fatigue as one of their top three most distressful symptoms [8]. For patients with Huntington's Disease (HD), fatigue is highly prevalent, with 82.5% of patients reporting the burden of fatigue [9].

"Clinical Methods: The history, physical and laboratory examination. 3rd edition" defines the scope of sleep disturbances as follows: "sleep disturbances encompass disorders of initiating and maintaining

sleep (…), disorders of excessive somnolence (…), disorders of sleep-wake schedule, and dysfunctions associated with sleep, sleep stages, or partial arousals" [10]. Sleep disturbances are also highly prevalent in many patients with chronic conditions and correlate with alterations in Activities of Daily Living (ADL) and Health Related Quality of Life (HRQoL). For example, in patients with HD, depression and cognitive impairment are associated with sleep and circadian rhythm alterations [11]. Furthermore, sleep disturbances are also common in IMIDs, with sleep disruptions worsening the symptoms of IBD [12].

Patients with PD are often diagnosed with sleep disorders. These symptoms are among the first experienced at the onset of the disease, and the majority of patients with overt clinical manifestation of PD present alternations in their sleep behaviour [13]. The most frequent sleep disorders among PD patients are insomnia, daytime sleepiness with sleep attacks, restless-legs syndrome (RLS) and REM-sleep behaviour disorder (RBD) [14]. This is partly influenced by the disease pathophysiology (neurodegenerative processes within sleep brain circuitries), medication treatment (antiparkinsonians acting as agonists on dopamine receptors, antidepressants), and co-morbidities [14].

While fatigue and sleep disturbances are common symptoms across a range of chronic conditions, the underlying mechanisms of these symptoms vary across these conditions, increasing the complexity of managing and treating such symptoms. Moreover, the relationship between fatigue and sleep disturbances is complex, and up to date poorly investigated.

4.2 Assessment, treatment, and care pathways

There are no specific care pathways for the assessment and treatment of fatigue and sleep disturbances[1]. Most patients experiencing fatigue usually reach out to their primary physician or specialist concerning their underlying disease (IMIDs, NDDs, oncological issues). In clinical practice, physicians typically ask whether patients feel tired or fatigued. Understanding of the concept varies across patients and physicians, as there is no "gold standard" for measuring it. Some physicians proactively ask all patients if they feel tired and how they "get rid of the tiredness". Yet, given that patients experience many different symptoms, it is exceptional that this symptom is addressed so explicitly. If signs of fatigue are detected via this questioning method, questionnaires are recommended to understand the severity and impact of fatigue. Even though these have been developed and are recommended in specific clinical guidelines, they are still not employed as a standard practice. Clinicians understand that this is not sufficient as there is not an exhaustive model of fatigue.

Current ways of measuring fatigue include Patient Reported Outcomes (PROs) captured via specific scales. However, these scales often lack multi-dimensionality. For example, the Fatigue Severity scale [15] includes only one question assessing "mental fatigue". The scales are often unable to capture variability often experienced by patients and do not measure both severity and impact of fatigue. Furthermore, scales measuring fatigue ought to be validated for specific patient groups.

Scales are often used in the context of clinical studies. Examples of questionnaires widely used include Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) for assessing fatigue, Depression in Old Age Scale (DIA-S) or Beck Depression Inventory to assess depression. To assess apathy, the Apathy Evaluation Scale (AES) or the Patient Reported Outcome Measurement Information System Fatigue Short Form Questionnaire (PROMISE F-SF) fatigue questionnaires could be used[2]. Different questionnaires are utilised to assess fatigue and sleep disturbances across disease

[1] There are a few clinics that have started offering services in the UK. They primarily address patients diagnosed with chronic fatigue syndrome. This is not necessarily applicable to most of patients suffering from fatigue.

[2] Source: expert interviews

areas (i.e., NDD vs IMID). For example, fatigue in IBD can be evaluated with the Fatigue Severity Scale (FSS) and the (Daily or Modified) Fatigue Impact Scale (FIS) [16]. For the assessment of fatigue in PD patients, there is a variety of scales that are commonly used, i.e., FSS, FACIT-F, the Parkinson Fatigue Scale (PFS), the Visual Analog Fatigue Scale (VAFS) [8].

Polysomnography (PSG) is the gold standard in diagnosing sleep disorders [17]. Despite the insights it provides, PSG requires time and resources to be conducted [18]. Moreover, it is challenging and inconvenient to follow the impact of the sleep problem over time[3], and it establishes an artificial setting for the patients [20]. In fact, the European Medicines Agency corroborated the importance of measurements in natural settings by suggesting that "clinical studies focussing on these symptoms [of insomnia] should be performed in the natural setting of affected patients" [19].

Assessment of sleep disturbances and sleep quality in IBD is multifactorial and can involve the evaluation of several variables, including sleep duration (number of hours spent sleeping), sleep latency (how long it takes to fall asleep), sleep efficiency (hours asleep in bed compared with time spent in bed), and number of sleep arousals (sleep fragmentation). Sleep disturbances can be characterised by chronic sleep deprivation, primary sleep disorders (insomnia, restless leg syndrome, periodic limb movement disorder, and obstructive sleep apnoea), and secondary sleep disorders (due to other medical conditions) [20]. Studies on sleep disturbances in IBD report a higher prevalence of fragmented sleep in patients [21] and a correlation between symptoms and quality of the previous night's sleep [22]. They also report on the association of sleep disturbances with IBD disease activity, including subclinical inflammation and the risk of disease relapse [23]. More than half of the patients included in a study of IBD reported poor quality of sleep, which emphasises its high prevalence in patients with IBD [4].

In addition, similar to fatigue, sleep disorders are reported to be frequent, even when the disease is in remission [24], with a strong consistent association between poor sleep quality and the presence and severity of fatigue. To assess sleep disturbances, QoL and sleep quality are often assessed using the IBD Questionnaire-Short Form (IBDQ-9) and the Pittsburgh Sleep Quality Index (PSQI), respectively [4].

To diagnose sleep disorders in NDDs, health and care professionals recommend validated questionnaires such as the PSQI or the Medical Outcomes Study Sleep Scale (MOS). To detect sleep disturbances in PD specifically, the Parkinson's disease sleep scale (PDSS) tool is used [14]. The evaluation of daytime sleepiness can be performed by using Epworth Sleepiness Scale (ESS), the inappropriate sleep composite score (ISCS) or the Stanford sleepiness scale (SSS). These questionnaires are recommended to be used in addition to reviewing the patient's medical history and potential referral to sleep specialists for further investigations [14]. In the case of NDDs such as PD, however, there is no standard treatment for managing sleep disorders. It usually starts with optimisation of the dopaminergic medication, followed by specific treatment of the identified sleep disturbances [14].

In summary:

- Fatigue and sleep disturbances are highly prevalent symptoms in many chronic conditions
- These symptoms are highly variable and unpredictable, and several confounding factors are present
- Measurements are usually performed via PRO Questionnaires that lack specificity and sensitivity
- There are no specific care pathways or treatments to address these symptoms

[3] Source: expert interviews

Furthermore, current limitations of the assessments of symptoms and progression of NDDs and IMIDs contribute to high failure rates and cost of clinical trials, impeding the progress in therapeutic development for these conditions and hampering the optimal management of patients.

4.3 Digital endpoints

To address the challenges in measuring and treating fatigue and sleep disturbances, as laid out above, digital technology and digital endpoints specifically may provide a novel way of measuring fatigue and sleep disturbances more accurately and reliably. The term "endpoint" refers to health measurements utilised for "the assessment of health and disease [which] requires a set of criteria to define health status and progression", whereas "digital endpoint" is defined by its use of sensor-generated data often collected outside of a clinical setting such as in a patient's free-living environment" [25].

Improvements in digital endpoint technology and the utilisation of digital endpoints will enhance regulatory recognition of digital mobility assessment as a critical secondary or primary endpoint for clinical trials, enabling both digital assessment and drug development to progress [26].

IDEA-FAST approach to development of digital endpoints

To develop digital endpoints that address fatigue and sleep disturbances, IDEA-FAST adopted the Clinical Trials Transformation Initiative (CTTI) approach[4] [27] and consequently defined several concepts of interest (COIs), i.e., characteristics impacted by fatigue and sleep disturbances. As these symptoms are highly complex and multifaceted, multiple COIs are needed to provide a more accurate assessment. The COIs pertain to the following five domains: 1) physical activity, 2) physiology, 3) neurophysiology, 4) neurocognition, 5) social function and interaction. Further, examples of candidate digital endpoints to assess these dimensions of impact of fatigue and sleep disturbances were proposed. Each COI was operationalised and mapped to digital devices and technologies, as presented in the figure below.

[4] The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership aimed at making clinical trials "patient-centred & easily accessible, fully integrated into health processes, designed with a quality approach, maximally leveraging all available data, improving population health" by 2030.

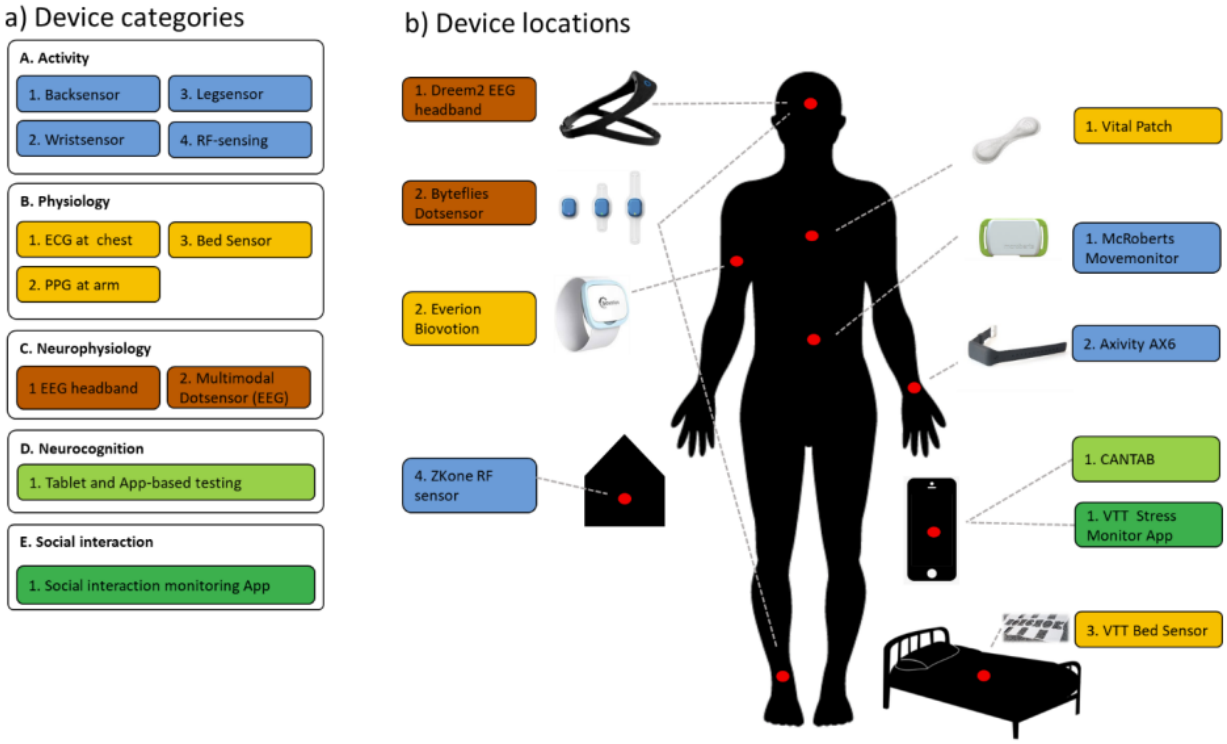


Figure 1 Device categories (a) and the actual devices and their locations (b) utilised in the IDEA-FAST feasibility study. Source: D4.1 Definition of Assessment Protocol [28].

The COIs were appraised in an initial Feasibility Study (FS) and will be validated in a follow-up Clinical Observational Study (COS) with approximately 2000 participants. The digital endpoints developed and validated in the IDEA-FAST project are intended to be sustained for use in research and clinical care beyond the funding of the project.

5 Use cases for the implementation of digital endpoints

In the context of socioeconomic evaluation and exploitation, use-cases support and facilitate the identification of relevant actors and systems involved, as well as the process(es) that are ongoing or need to be changed to better achieve new projected outcomes or goals. They also support selecting what might be appropriate methods, tools, and measurements to identify the expected or realised changes in achieving the project's objectives. In this section, two key use-cases for the implementation of digital endpoints are described:

- Clinical research: interventional clinical trials & observational cohort studies
- Clinical routine care

5.1 Clinical research: interventional clinical trials and observational cohort studies

Digital technologies transform health and care settings while setting the basis for highly patient-centric innovation in the pharmaceutical industry. In clinical studies, the use of digital endpoints has the potential to drive innovation and reduce costly late-stage failures [26]. Digital clinical trials represent a novel way for clinical trial implementation as they use technology to improve recruitment and retention, data collection, and analytics [29] (Figure 2). Furthermore, as digital biomarkers are used more frequently, clinicians will be able to employ different means of gathering clinical insights remotely. The integration of the tools depends in part of design studies that are considered in decentralised clinical trials [30].

The COVID-19 pandemic has accelerated the shift from fully centralised to hybrid and decentralised clinical trials. While fully decentralised clinical trials are not very common and are of observational, rather than experimental nature, pharmaceutical companies reported that there were significant changes in the number of remote assessments performed due to illness or restrictions, both for staff and patients, and it is believed that hybrid trials will be more common in the future. Hybrid and fully decentralised clinical trials are further assumed to alleviate biases associated with PROs, as they will most likely rely on digital technologies for more objective measurements. As a result, it is expected that fewer clinical trials will fail. Digitisation will support streamlining clinical trials costs and efforts by using digital technologies and, at the same time, creating a patient-centred trial experience.

Furthermore, trial efficiency can be improved by enhancing and supporting the role of investigators and study teams and by creating opportunities for real-time, remote monitoring and interactive patient management and assessment. A fully digital trial will be able to build equity and access for potential participants regardless of their location. In 2019, Janssen launched its first entirely digital clinical trial [32], marking the first-ever completely decentralised, mobile, indication-seeking clinical study.

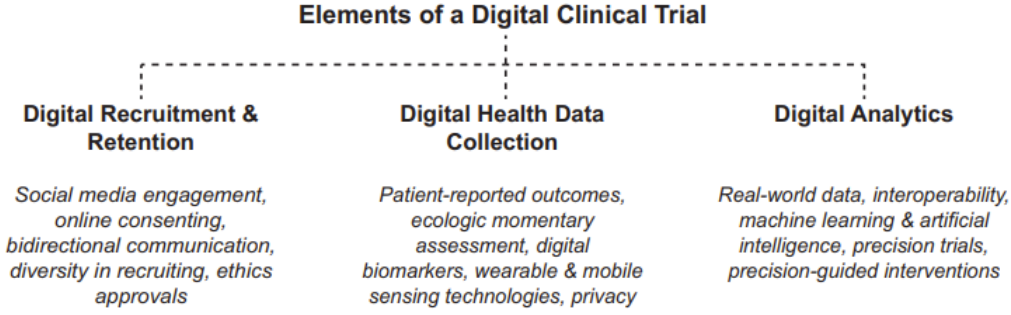


Figure 2. Elements of a Digital Clinical Trial. Source: Inan et al., 2020 [29]

Based on interviews conducted by Deloitte [31], Figure 3 summarises applications of digital solutions in clinical trials and how digital innovation can be utilised in clinical development processes.

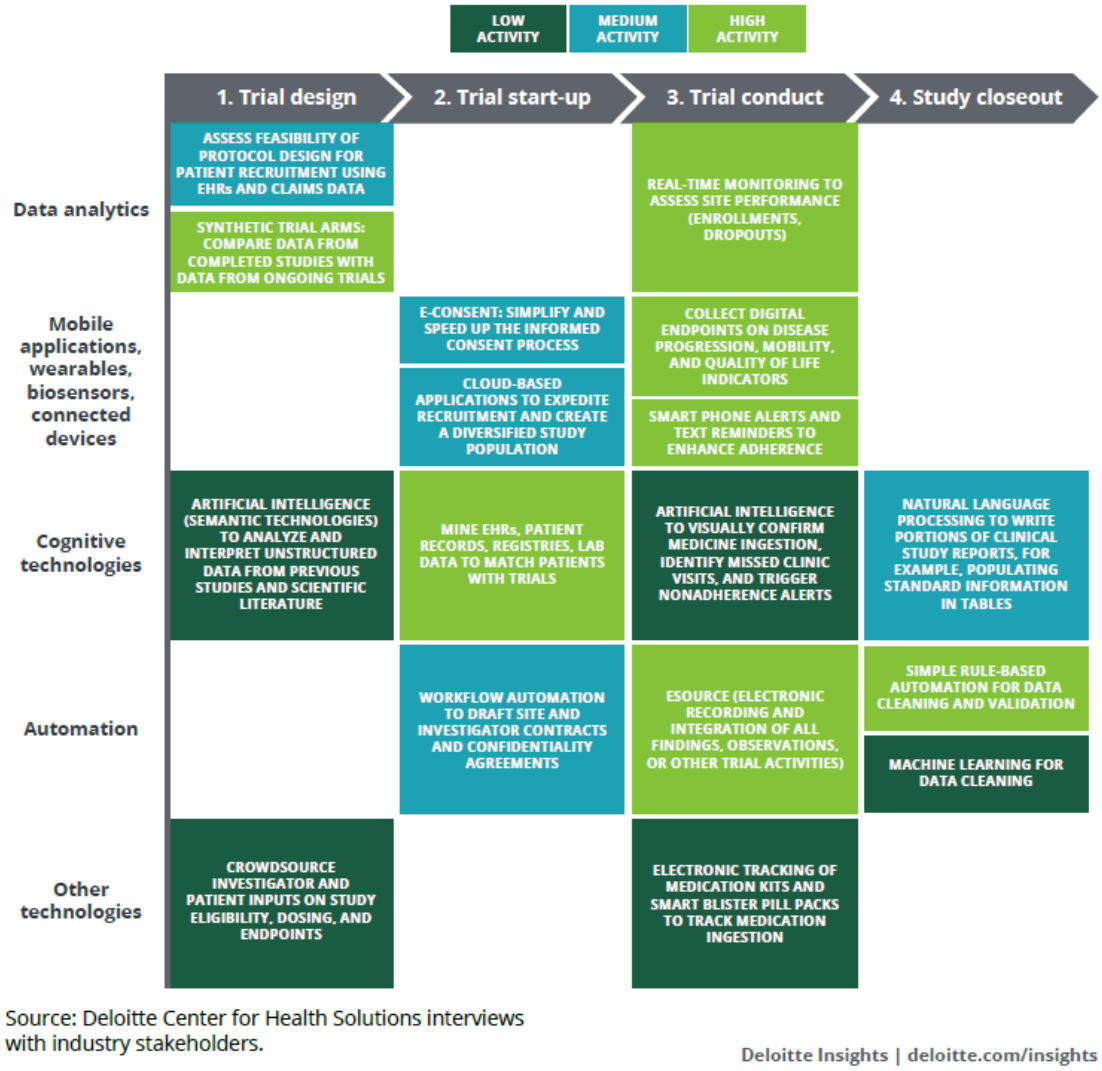


Figure 3. Applications of digital solutions and innovations to clinical trials. Source: Anderson, D., Fox, J., and Elsner, N., 2018 [31].

IDEA-FAST contributes to the digitalisation of clinical trials, mainly through the development of the novel digital endpoints for assessing fatigue, sleep disturbances and ADLs. Through the implementation of the digital endpoints, clinical trials will be supported at multiple dimensions:

- ✓ Increased objectivity of results

Complex composite digital endpoints will lead to a higher sensitivity, specificity, and objectivity of measurements compared with clinical rating scales. Furthermore, measurements performed in the patient's natural environment will increase the ecological validity of the results. More accurate measures imply smaller sample sizes and ultimately faster benefits for patients by delivering treatments sooner (a drug takes 12-15 years of research until it reaches the market).

- ✓ Inclusive studies and increased diversity, patient-centric approaches

Implementation of digital endpoints that allow home measurements will increase participation rates and enable trials to be conducted in vulnerable populations with chronic diseases (e.g., elderly, psychiatric patients) that may be underrepresented in clinical research due to various factors, such as lack of mobility, ethical barriers, and low recruitment rates [33].

- ✓ Novel insights

This will also enable the chance to derive novel insights from populations that do not comply well with the lab settings, such as children diagnosed on the autistic spectrum. These groups are highly sensitive and prefer environments they already are familiar with; therefore, conducting a study in their natural settings might generate different insights than a standard clinical trial performed at a research centre.

- ✓ Early safety issues

The collection of dense physiological data may identify early safety issues, inform dose adjustments and dosing frequencies or lead to the discontinuation of the development of specific drug candidates [34].

- ✓ Patient recruitment

Patient recruitment is perceived as an area where digital endpoints could play a significant role in the shift to decentralised/hybrid clinical trials, as the measurements will be conducted in the patients' home setting. The expected benefits of decentralised and hybrid trials include lower attrition rates, as some barriers such as distance can be overcome. They can further help tackle educational barriers with digital devices and enable telehealth to correct behavioural elements. Moreover, it is assumed that partially digital trials can be more efficient than traditional clinical trials as researchers can closely monitor the study participants.

- ✓ Increased market size and establishing new markets for drug development

Fatigue and sleep disturbances are prevalent in many chronic conditions. Digital endpoints could contribute to faster drug development across a plethora of therapeutic areas, e.g., CNS (including neurodegenerative disorders, chronic fatigue syndrome/Myalgic Encephalomyelitis), Immune-mediated disorders (e.g., IBD), Oncology (e.g., cancer fatigue). Some pharma representatives reported that whereas fatigue and sleep disturbances are not currently a separate research area, showing that a drug alleviates these symptoms in a specific disease area is highly important overall. As a result, pharmaceutical markets will be strengthened and enlarged. Since fatigue and sleep disturbances heavily impact the ADL and QoL, they are a critical outcome to patients. Furthermore, establishing specific digital endpoints will open the possibility of establishing new markets for drug development.

- ✓ Overall cost savings

All previously mentioned benefits of using digital endpoints in clinical trials ultimately contribute to the significant reduction of clinical trial costs. Furthermore, the possibility of more quickly gathering the data necessary to determine if the drug is effective or not can enable funds to be redirected to other research projects and studies. However, the overall potential reduction of costs still needs to overcome certain regulatory burdens, as regulators still require traditional data, such as patient-reported outcomes, in addition to the data collected by the devices. According to the current model, "new" data presents an add-on that will bring additional costs to the existing ones. Nevertheless, partners highlighted that patient-reported outcomes ought to be collected and emphasised the opportunity to reduce costs through economies of scale.

Perceived barriers

Perceived barriers towards the implementation of more hybrid and decentralised trials mentioned by pharmaceutical company representatives are related to mindset and leadership culture, lack of support

mechanisms around digital devices (e.g., clinical research organisations, multiple languages, scale), socio-economic aspects (e.g., there is a risk of excluding groups when conducting research in a "bring your own device" model), stable data connection, the need to ensure continuous service, as well as training. In hybrid and decentralised trials utilising digital devices, pharma companies prefer renting digital devices due to the fast development and change of devices and technologies. Additionally, the cleaning, upkeep and storage of devices are associated with additional costs. Traditional healthcare institutions, which are usually paid by the number of study participants or tests they perform, could potentially lose revenue as they might be less involved.

5.2 Clinical care: health and care provision

The use of digital endpoints is not limited to clinical studies. In the past, quantification of clinical outcomes in real time was impossible, therefore assessments were done retrospectively on huge clinical studies. However, with the introduction of the Internet of Medical Things (IoMT), this situation is changing. Now, outcomes can be monitored on an individual level in real time alongside a novel medical intervention, either before, i.e., in clinical studies, or after it is released to the market. Future clinical outcomes can therefore be monitored in the context of value-based care[5] using programs that track activity, efficacy, and safety [26]. For example, home monitoring of asthma symptoms via an electronic questionnaire has been shown to reduce the need for outpatient clinic visits [35], and including objective measurements with wearable or portable devices may further improve the reliability of home monitoring [36]. Implementation of validated digital endpoints for sleep disturbances will also reduce the need to rely on traditional polysomnography assessments.

Current clinical endpoints used in assessing fatigue and sleep disturbances rely heavily on subjective reports, capturing PROs using standardised questionnaires such as the FSS. The approach has many limitations, including being more prone to recall bias, reliability issues and poor sensitivity to change. As PROs are being collected at low frequencies, they only partially capture the variability of the measures over time. Furthermore, some patients might present cognitive and affective dysfunctions, putting into question the reliability of the self-assessed data. Many patients with fatigue and sleep disturbances report substantial variations in the severity of their symptoms over time. This variability is often difficult to be quantified accurately, presenting itself as a challenge for clinicians to fully assess the symptoms, their impact and the efficacy of any interventions prescribed for the symptoms. The ability to assess these symptoms quantitatively and over a prolonged period in their habitual environment through the implementation of digital endpoints has the potential to improve clinical care pathways by [30]:

- ✓ Supporting the diagnosis of challenging patients
- ✓ Enhancing stratification of patients into risk categories
- ✓ Serving as pharmacodynamic response markers
- ✓ Providing monitoring in addition to or in place of traditional visits to the outpatient clinic
- ✓ Aiding in the prediction of health outcomes after hospital admission.
- ✓ Increasing the reliability of symptom assessments

In conclusion, digital endpoints have the potential to help clinicians to perform a more valid and complete assessment of the impact of diseases and treatments, facilitate better clinical management, and promote patient-centred care and personalised medicine.

[5] Michael Porter defines value-based healthcare as value as outcome divided by costs of a healthcare intervention.

6 Stakeholder classification and mapping

The use cases presented above highlight how the implementation of digital endpoints may impact both clinical research and clinical care. Against the background of the selected use cases, actors, users, and stakeholders most affected need to be defined to develop a socioeconomic evaluation framework for estimating potential impacts.

A vital design step for any impact assessment and exploitation model is identifying and specifying the stakeholders involved. This requires an account of the actual people and organisations concerned, which can initially be classified into generic, high-level stakeholder groups and, eventually, smaller-size sub-groups. A more detailed stakeholder analysis ensures that the full impact of outcomes is reflected in more detail in the evaluation, which in turn is usually more helpful for better targeting policy interventions to optimise impacts.

Mechanism design theory [37] and participatory usability evaluations take as their basic premise the view that technology developments should be driven by user requirements rather than technological capabilities. Thus, a starting point for usability evaluation and systems design is to understand the user population, but also the general stakeholders, in some detail.

Extending the concept to IDEA-FAST, for the purpose of this deliverable and the assessment approach, users are understood as actors who consume products or services enhanced by digital endpoints (e.g., data management platforms, clinical decision support tools, etc.). ‘Stakeholders’ then refers to the broader group of actors with a vested interest in the outputs and developments of the digital endpoints, including patients, healthcare professionals, pharmaceutical companies, national competent authorities, healthcare providers, and the research community. Assessment perspectives based on stakeholders are most important as they guide the overall assessment process: the results must be useful for them and, as required, also helpful for those who influence or take systematic decisions. From this, it follows that the respective perspective should (1) govern the methodology of the assessment framework such that (2) it allows one to measure the effect a technology can have on a range of actors.

The following stakeholder groups were identified as being pertinent to the IDEA-FAST context:

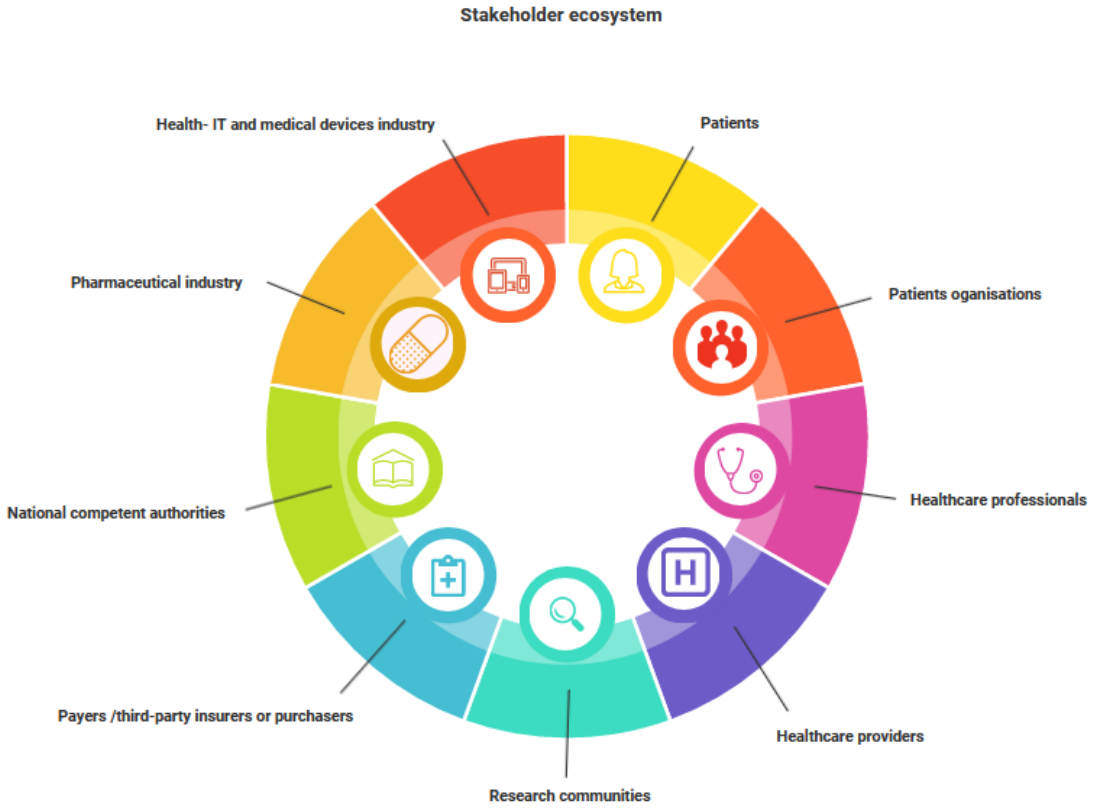


Figure 4. Key stakeholders that may benefit from or use the digital endpoints developed in IDEA-FAST. Source: empirica.

- Patients

For many new developments in the healthcare domain, the individual patient is often envisioned as the ultimate beneficiary. Similarly, patients are key users and beneficiaries for whom the development of digital endpoints for sleep and fatigue disturbances would lead to better monitoring and treatment options, as described previously.

- Patient organisations

Patient organisations, especially those with strong engagement in the clinical side of research and treatment, are identified as important actors supporting patient participation within the project, both in terms of the clinical validation studies as well as the dissemination of developments.

- Healthcare professionals

This group encompasses nurses, general practitioners, sleep specialists, mental health professionals, and other specialists (e.g., NDD, IMID). As previously described, the implementation of digital endpoints to measure fatigue and sleep disturbances offer professionals better tools for addressing fatigue and sleep disturbances in their patients, thereby making them central actors for the ‘‘buy-in’’ of new related developments, especially in terms of utilising these tools.

- Healthcare providers

This group is comprised of healthcare provider organisations such as hospitals and clinics. These organisations aim to provide excellent and safe care, at a reasonable cost, to a large number of patients.

They aim to avoid the expenditures and hazards related to healthcare delivery determined by using diagnostic systems or processes with uncertain reliability, value, and safety. As for other patients and healthcare professionals, the development of clinical tools based on digital endpoints would offer these organisations better means of addressing their patients' needs in a more cost-effective and scalable manner. Consequently, healthcare-providing institutions in today's digital environment are also interested in upholding their reputations and developing competitive advantages; integrated digital health systems, of which digital endpoints would be a component, offer an avenue for this purpose.

- Payers / third-party insurers or purchasers

Third-party insurers, payers and purchasers all desire low delays and waiting times for patients, short hospitalisation times, no expensive re-admissions for issues (including revisions), and a rapid return to work. The insurers' goal is to deliver equal advantages to all customers while staying within their budget. The type of payer depends on the healthcare system at hand (e.g., Bismarck vs Beveridge). Whereas Germany, a Bismarck healthcare system, has statutory health insurance (SHI) and private health insurance (PHI) institutions, the UK, a Beveridge system, has a national healthcare system (NHS). Third-party insurers, payers and purchasers could benefit from cost savings derived from the use of digital endpoints. Furthermore, the implementation of digital endpoints may also provide information and evidence for reimbursement decisions (e.g., coverage of a new medical device or clinical tool conditional on validated evidence).

- National competent authorities (NCAs)

Policymakers, such as public health authorities and regulators, are concerned with the general welfare of the public. As a result, they require data on overall clinical activity for public health objectives, needs assessments, and healthcare macroeconomic policy planning. Public health organisations also want to ensure that the institutions under their control deliver high-quality, problem-free healthcare to the general public. National and international regulatory organisations play a vital role in overseeing digital health systems, ensuring that the technologies are safe, efficient, and reliable for public use. NCAs rely heavily on the evidence obtained by clinical studies such as those conducted in IDEA-FAST as part of their health technology assessment processes. Within the IDEA-FAST context, NCAs are stakeholders as they decide on policies related to the reimbursement and use of digital endpoints. Decisions made by such organisations play a role in shaping the acceptability of digital endpoints in routine clinical care.

- Pharmaceutical industry

The pharmaceutical industry's primary focus is on the development of new therapies. The use of digital endpoints to measure fatigue and sleep disturbances results in added value in the context of clinical trials conducted by pharmaceutical companies. Digital endpoints would enable decentralised and hybrid models of clinical trials that offer advantages such as more accurate results, increased outcome sensitivity, shorter trial duration and better inclusion for study participants who might feel uncomfortable in traditional study settings away from their known surroundings, such as people with autism or neurodegenerative diseases. For pre- and post-market authorisation, reimbursement, and procurement processes, the pharmaceutical sector collaborates with and is reliant on various stakeholders such as healthcare providers, regulators, and payors insurance companies.

- Health-IT and medical devices industry

IDEA-FAST provides results in terms of the clinical validation, feasibility, and acceptability of digital endpoints for fatigue and sleep disturbances. Implementation and regulatory recognition of these endpoints would profit the health-IT and medical devices industries upon whose solutions and devices the digital endpoints are based.

- Research community

The research community (academia) is engaged with increasing knowledge and producing evidence to find solutions both for existing healthcare concerns and to be able to predict or prevent future ones. Beyond this perspective, research extends to sociological, political, and economic viewpoints in addition to health domains. The research community has the capability of bringing stakeholders together and translating research on digital endpoints for fatigue and sleep disturbances into understandable and actionable knowledge for decision-makers and implementers. As highlighted in the previous section, the use of digital endpoints also offers researchers novel ways to conduct clinical trials and develop new scalable outcome measures for their objectives.

7 Socio-economic evaluation

To provide evidence supporting the key benefits of implementing digital endpoints in clinical research and clinical care, a socio-economic evaluation with respect to the various stakeholders identified above is needed to measure the expected "impact". Impact is defined in this deliverable as any perceived benefits or costs these actors may be confronted with. These terms must be understood in a broad meaning encompassing benefits and costs expressed directly in monetary terms and any immaterial impacts that will influence decisions to develop and sustain, use, or finance such developments.

The theoretical foundations of the proposed socio-economic evaluation methodology are grounded in Michael Porter´s Value Chain Concept [38] and the concept of value added [39]. Value added in economics is the additional value resulting from transformations of factors of production into a ready product. At its simplest, it is the difference between the value of a product and the aggregate value of its individual components. Over the last decades, value added has been a widely used approach supporting decision making on investments and resource usage.

In the IDEA-FAST context, socio-economic impact can be defined as both the value added as perceived by various actors individually, and as the overall value, including external effects, added to society as a whole from the implementation and use of digital endpoints. This standpoint, called the social planner's perspective, encompasses the impacts on all affected actors [40]. The value added equals the total value of a service provided with the support of digital endpoints less the total value of a service provided without this kind of support.

value added from IDEA-FAST and digital endpoints = value of services with IDEA-FAST and digital endpoints – value of services without IDEA-FAST and digital endpoints

This societal perspective includes all stakeholders and aggregates their respective gains and losses, or benefits and costs. Positive effects, or benefits, create value. Negative effects, or costs, occur when value is reduced. The total value added is the sum of positive and negative 'value added', also referred to as net benefit. This societal perspective can be disaggregated into the benefits and costs of each stakeholder group. Furthermore, what may be a benefit to one group may be a cost to another group, and in the aggregate, some of them may cancel out. The analysis must expose these shifts in value to provide a reasonable account of the impact on individual stakeholders as well as society as a whole. Based on such considerations, qualitative cost-benefit analysis (qCBA) is proposed as the working paradigm with which to assess the socio-economic impact of IDEA-FAST and digital endpoints as an alternative to conventional cost-benefit analysis (CBA). The qCBA paradigm attempts to monetise as many of the project's effects as feasible while allowing for additional numerical metrics to quantify the other impacts [41]. For impacts and outcome measures where quantitative evaluation is not possible, the relative significance and magnitude of expected change of the impacts are estimated qualitatively [42]. A qCBA is particularly suited for socio-economic evaluation of a project such as IDEA-FAST where the impacts of multiple factors with different values needs to be assessed.

The following sections of this chapter present costs associated with the IDEA-FAST use cases, namely those related to clinical trials and those of the burden of fatigue and sleep disturbances on society. Chapter 7.2 further discusses the association between sleep deprivation and ill health, its significance specific to NDDs and IMIDs, and the resulting direct and indirect costs for patients, healthcare systems, and society as a whole. Within this paradigm, direct costs refer to the monetary consumption of health system resources due to treatment, prevention, or rehabilitation, including factors such as medication for sleep disturbances or fatigue, medical consultations, or related administrative costs.

Indirect costs refer to the tangible and intangible loss of resources resulting from sleep disturbances, disorders, or fatigue, such as work absence, physical and mental ill-health, accidents, loss in productivity and QoL. As the aim of the IDEA-FAST project is to identify and validate digital endpoints of fatigue and sleep disturbances, impaired ADL, disability, and HRQoL for the evaluation of therapeutic interventions, these tangible and intangible costs can be translated into benefits resulting from resource liberation when treating patients more effectively and efficiently.

Generally, it should be noted that the cost research presented in this chapter is primarily derived from articles referencing ICD-10 codes referring to fatigue and sleep disturbances, respectively. As fatigue and sleep disturbances are often not sufficiently recognised and their prevalence was exacerbated by the recent COVID-19 pandemic[43], it is expected that the costs presented in this chapter are lower than the actual costs that occur due to fatigue and sleep disturbances across a plethora of diseases.

7.1 Costs of clinical trials and related studies

According to a recent Deloitte report on measuring the return from pharmaceutical innovation in 2020, costs to bring new therapies to market continue to increase due to the growing complexity of development and longer cycle times [44]. Estimates for the average cost of bringing new therapies to market vary between $800 million and $2 billion, where highest price components are represented by late-stage failures and rising costs of Phase II and III trials [45]. As pharmaceutical spending [46][6] covers between 6.8% - 34.4% percent of health spending [46], any efficiencies in the drug development process may contribute to accelerating new treatments, while also lowering pharmaceutical companies operating costs which can offer opportunities for lower pricing to patients, governments, and health care systems.

A core concern and barrier to drug development and conducting clinical trials is represented by the high costs, with rising trial costs due to the complexity of clinical development programmes. Increased regulatory scrutiny, safety and efficacy evaluation and the need to demonstrate the value and efficacy of a drug compared to an already established treatment contribute further to the rise of drug development costs.

Bio-pharmaceutical and medical device companies are the ones who usually initiate clinical trials and, in many cases, are also the primary financial sponsors of the trials. A landmark study conducted by the KMR Group in 2016 assessed clinical trial costs across seven major pharmaceutical companies [47]. The detailed data collection process enabled total trial costs to be broken down by key cost areas within each trial: personnel, outsourcing, grant/contract and other expenses. Personnel spending represented 37% of the total costs for the average phase III trial, whereas outsourcing and grant/contracts spending each make up approximately one-fifth of the total trial cost. The median cost of conducting a study from protocol approval to the final clinical trial report was US$3.4 million for phase I trials involving patients, $8.6 million for phase II trials and $21.4 million for phase III trials. Trial protocol design choice and factors such as the number of subjects, sites and visits increase the variability of the costs. An increased number of countries helps broaden patient populations, yet they raise challenges by expanding timelines of increasing costs of clinical trials. The trial duration is also highly relevant when considering significant costs, where each additional month for phase III trials translates into a median of $671,000 spent. The study argues that even small cycle-time reductions could have meaningful benefits on overall clinical development budgets. Three groups of factors that can be targeted to improve cost performance (see Table 1) are:

[6] Pharmaceutical spending covers expenditure on prescription medicines and self-medication. Pharmaceuticals consumed in hospitals and other health care settings are excluded.

- choices for trial design parameters (e.g., size of study, number of endpoints and treatment duration)
- operational choices (e.g., outsourcing and use of emerging markets)
- cycle-time reductions

Table 1. Influence of selected factors on clinical trial costs. Source: KMR Group

Factor	Description	Total trial cost
Sites	Number of sites randomising	Significantly increased
Subjects	Number of subjects randomised	Significantly increased
Visits	Number of subject visits	Significantly increased
Duration	Duration of trial (time from protocol authorisation to final clinical trial report)	Significantly increased
Molecule size	Large versus small molecules	Not significant
Rare disease	Rare versus non-rare disease	Not significant
Adaptative design	Adaptative versus non-adaptative design	Not significant
Emerging market activity	Emerging market activity versus no emerging market activity	Significantly increased
Emerging market subjects	Percentage of subjects in emerging markets	Significantly increased
Regions	Number of regions	Significantly increased
Countries	Number of countries	Significantly increased

The implementation of digital endpoints would likely lead to a significant decrease of clinical trial costs, as decentralised trials would require significantly fewer research sites employed, fewer subjects (as the measurements will be more sensitive, the required sample size might be smaller) and the overall total duration of the trial would be significantly decreased.

7.2 Costs of the burden of disease

Fatigue and sleep disturbances are highly prevalent and associated with direct and indirect costs for patients and society. Their presence across populations with different health conditions is considerable [48, 49], thus highlighting the relevance for public health. Insufficient sleep negatively impacts physical and mental health [50] and consequent societal and healthcare costs.

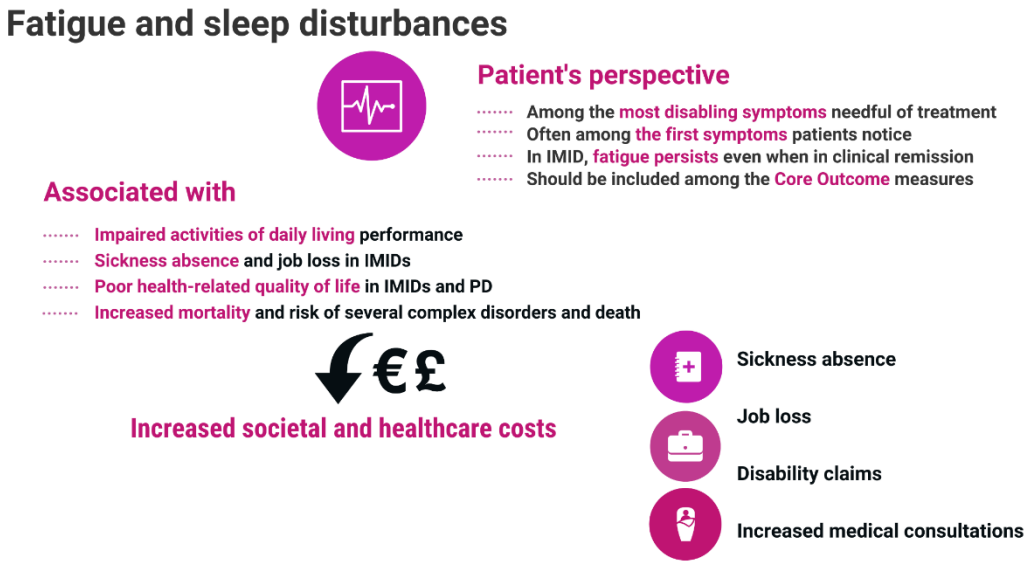


Figure 5. Fatigue and sleep disturbances are highly prevalent and associated with increased societal and healthcare costs. Source: empirica

Previous research among five OECD countries identified that those sleeping less than six hours per night have a 13% higher mortality risk and a substantial loss of working time compared to those sleeping between seven and nine hours [51]. Accordingly, employed individuals with insufficient sleep of fewer than six hours per night have, on average, a 2.4% higher loss in productivity than those sleeping seven to nine hours due to more absenteeism and presenteeism, resulting in reduced performance. This is also visible among those sleeping between six to seven hours, with an average 1.5% higher productivity loss. Consequently, an individual with insufficient sleep loses around six working days out of 250 working days per year more, compared to workers sleeping more seven to nine hours [51].

Studies among NDD and IMID patients demonstrated that fatigue and sleep disturbances worsen patients' QoL [52, 53]. However, quantification of the costs due to loss in QALYs or DALYs specific to fatigue and sleep disturbances are scarce in the literature. Therefore, identifying and validating digital endpoints for fatigue and sleep disturbance and their impacts on patients' HRQoL is crucial.

The multiple physical and mental health conditions associated with fatigue and sleep disturbances, including chronic diseases, are linked with high healthcare usage. At the same time, affected patients with fatigue consume more healthcare resources than those without fatigue, resulting in substantially higher costs. Therefore, it can be assumed that effective, personalised treatment of fatigue and sleep disturbances can substantially benefit patients, healthcare providers and health systems at large. Table 2 below presents the specific costs, categorised as direct or indirect, of fatigue and sleep disturbances as applicable to three selected stakeholders, namely patients, healthcare providers, and insurers.

Table 2. Potential direct and indirect cost of fatigue and sleep disturbances for different stakeholders

Stakeholder	Direct costs	Indirect costs
Patients	• Inpatient care and rehabilitation • Outpatient care and rehabilitation • Diagnostic tests • Medications • Psychological therapy • Other (e.g., health insurance, alternative medicine, emergencies, community healthcare services) • Transport related to medical consultations, diagnostic tests, treatment	• Loss in productivity • Impaired cognitive performance • Absenteeism and presenteeism • Loss of income (e.g., early retirement) • (HR)QoL and QALY decrement • Decreased ability to perform ADLs and participate in social activities • Increased disease activity and pain sensitivity • Co-morbidity (mental and physical) and mortality • Inconvenience of diagnostic tests (e.g., polysomnography in sleep laboratory) • Side effects of pharmacotherapy • Accidents (falls, road, occupational)
Healthcare providers	• Time and resources spent for provision of inpatient and outpatient healthcare services (medical consultations, diagnostic tests, treatment, rehabilitation) • Administrative costs	-
Insurers (payers)	• Administrative costs • Patient insurance claims, reimbursements • Payment of healthcare providers • Employee sick leave	-

The following analysis focuses on two countries involved with clinical sites in the IDEA-FAST project: Germany and England. These countries serve as an example of the possible benefits of implementing digital endpoints to assess fatigue and sleep disturbances in Bismarck and Beveridge Model healthcare systems, respectively. An overview of quantified costs and benefits in the two countries is provided in Table 5.

7.2.1 Fatigue and sleep disturbances in Germany

Prevalence

Sleep disturbances and fatigue are highly prevalent in the German population and continue to rise. According to a 2018 "forsa" study among German adults (n = 1,010), 15% suffered from sleep disturbances almost every night, and 20% experienced these often. As a result, 35% often felt tired and had difficulties concentrating during the day [54]. The DAK health insurance company estimated that around 34 million working people in Germany experience problems with initiating and maintaining sleep, and one in ten working individuals have insomnia[55]. Further, it is estimated that 20-60% of the general German population experience fatigue [56].

A BARMER report estimated that about 656,000 individuals in the German working population were diagnosed with non-organic insomnia (ICD-10 F51.0) or with disorders of initiating and maintaining sleep (ICD-10 G47.0) in 2017 [57]. Applying a more expansive definition and including unspecified sleep disorders (ICD-10 F51.9 and G47.9), it was estimated that about 1.55 million working individuals received a respective diagnosis. Additionally, an online survey among 4,000 participants found that 26% of respondents believed to suffer from a sleep disturbance, and 20.9% struggled with difficulties initiating and maintaining sleep. Data indicated that women were more frequently affected than men, and diagnoses rose with increasing age [57]. Similar results were obtained by van de Straat and Bracke [58], who identified sleep problem symptoms among 26.7% of respondents.

However, it can be assumed that the actual prevalence is higher since sleep disturbances are often not documented or diagnosed. Accordingly, a specific diagnosis is only given in about 27% of cases [59].

Direct costs

Total costs of illness

The German Federal Office of Statistics reported that, in 2015, the total costs of illness of non-organic sleep disturbances (ICD10-F51) amounted to €105 million and € 922 million for disorders of initiating and maintaining sleep (ICD10-G47) [59]. Out of the more than €338 billion total costs of illness in 2015, the costs of sleep disorders thus represent 0.3%. This calculation includes overall healthcare resource consumption related to the treatment, prevention, rehabilitation, and long-term care of specified disease and is the latest available data. Considering a broader definition of fatigue and sleep disturbances, many undocumented cases, despite the significant burden on NDD and IMID patients, as well as the associated co-morbidities, the implementation of personalised therapeutic interventions based on an assessment of digital endpoints can result in substantial savings for healthcare systems.

Hospitalisation and inpatient days

As indicated, direct costs for the German healthcare system also result from inpatient care for sleep disturbances. In 2018, there were 104,659 cases of hospitalisation with sleep disturbances (ICD10-G47) as the diagnosis, the vast majority of those being males (74,324 males and 30,371 females). On average, patients stayed in the hospital for two days, resulting in a total of 205,721 inpatient days. Of those cases, 16 died [60].

In Germany, patients above the age of 18 must co-pay €10 per inpatient calendar day for maximum 28 days per year [61]. This co-payment concerns hospitalisation and rehabilitative care and is capped at 2% of the patient's annual gross household income, or 1% for chronic patients. Taking the average of two days of inpatient care, patients in hospitals suffering from sleep disturbances would thus co-pay €20.

Diagnostics

Assessing digital endpoints of fatigue and sleep disturbances with digital devices that patients can use in their homes could reduce the number of unnecessary, costly inpatient diagnostic tests while increasing disease knowledge and enabling early intervention. SHI-insured patients are fully covered for sleep disorder tests, such as ambulatory polygraphy and inpatient polysomnography. If diagnostic tests require hospitalisation (i.e., polysomnography), patients only co-pay the inpatient days.

According to the DRG statistics, 104,327 polysomnography tests and 61,912 cardiorespiratory polygraphies were performed among hospitalised patients in 2019. Furthermore, a total of 4,536 multiple sleep latency tests (MSLT) or maintenance of wakefulness tests (MWT) were conducted in German hospitals [62]. Each night at a sleep laboratory costs the statutory health insurances about €500 [63]. The National Association of Statutory Health Insurance Physicians states that the cost of

cardiorespiratory polysomnography is €357.25 [64], whereas cardiorespiratory polygraphy costs €72.10 [65].

As mentioned previously, hospitals treating patients for sleep disturbances and performing diagnostics for sleep disorders are reimbursed based on the DRG system by multiplying the DRG cost weight with the base rate, including reimbursement for healthcare per inpatient day (federal base rate: 3,750 € in 2021):

- DRG E63A - sleep apnoea or polysomnography or cardiorespiratory polygraphy up to 2 inpatient days, age < 18 years or with a specific invasive cardiological diagnostic: 1,929.89 €
- DRG E63B - sleep apnoea or polysomnography or cardiorespiratory polygraphy up to 2 inpatient days, age > 17 years, without a specific invasive cardiological diagnostic: 1,280.61€ [66]

If the evaluation of therapeutic interventions through digital endpoints reduces inpatient days related to sleep disturbances and fatigue, this would, on the one hand, result in resource liberation, but, on the other hand, in income forgone for hospitals.

Doctor consultations

According to the Centre for Sleep Medicine & Sleep Research [67] patients having difficulties with initiating or maintaining sleep (e.g., insomnia) should consult a doctor if the sleep disturbances persist consistently for a minimum of four weeks, and/or if patients suffer from a significantly increased day-time fatigue.

However, BARMER indicated that less than half of affected individuals consulted a doctor, similarly to the "forsa" study showing that only one-third of those suffering from sleep disturbances almost every night have ever consulted a doctor [54, 57] A report from the Techniker Krankenkasse found that only one in ten insured individuals consulted a doctor for their sleep problems [68].

The National Association of Statutory Health Insurance Physicians calculates a flat rate for insured persons for a ten-minute consultation dependent on the patient's age, the EBM codes 03003-03005 refer to the adult population with a rate of €13.40 – 23.07 [69-71]. Furthermore, it is common for an additional flat rate of €15.55 to be added for the provisions of the structures necessary for a GP's office (code 03040) [72]. Moreover, surcharges are added for the GP's assistants (code 03060) and their surcharge (code 03061), amounting to €2.48 and €1.35, respectively [73, 74]. Based on these costs, a ten-minute GP consultation can range from €31.78 to €42.45, depending on the age of the patient.

Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is highly recommended as the first-line treatment of significant fatigue and sleep disturbances such as insomnia (CBT-I). In Germany, CBT-I is fully covered by SHI if it is administered by SHI-affiliated therapists, who receive €89.60 per one-hour session [75]. In the PHI, the reimbursement of therapy depends on the tariff conditions, so privately insured patients might have to pay for CBT-I partially or entirely out-of-pocket [76]. The costs of one session vary between €50-€150 [77].

According to the DAK insurance data among the DAK working population from 2016 (n = 2.6 million), 7.8% of individuals with a diagnosed sleep disturbance received psychotherapy [78].

Pharmacotherapy

In Germany, all prescription medication is covered by the SHI, but patients above 18 years of age must co-pay 10% of the sales prices. In all cases, patients pay a minimum of €5, and a maximum of €10 per prescription, ensuring that patients never pay more than the actual price of the pharmaceutical.

Furthermore, the total amount of supplementary payments are capped at 2% of the insured person's annual gross income. For chronic disease patients, the limit is set at 1% of annual gross income [79].

According to the German care pathway guidelines for sleep disturbances among adults, pharmacological therapy is only recommended if cognitive behavioural therapy is not effective or cannot be implemented. Treatment of insomnia with hypnotics (e.g., benzodiazepine receptor agonists) or sedative antidepressants should only be intended for short-term use, given potential side effects and risks [80].

Based on a DAK report, 22.1% of insured patients with diagnosed insomnia were prescribed pharmacotherapy, with one in five receiving an antidepressant and about 14% receiving a benzodiazepine. Notably, more than 20% of those with benzodiazepine prescriptions received those for one to three months, thus considerably longer than the recommended maximum of four weeks. The data also implies that pharmacotherapy is a dominant form of therapy compared to CBT-I as half of those consulting a doctor for their sleep problems were prescribed a sleeping pill [78].

However, these numbers only represent recorded prescriptions in the SHI, and the actual number of prescribed pharmaceuticals is potentially higher given increased private, off-record prescriptions of hypnotics [81]. This would also translate into substantially higher out-of-pocket payments for patients with private prescriptions.

Indirect costs

Macro-economic loss

Based on a macro-economic model considering increased mortality and work absence with decreased work and school performance, the RAND study [51] predicted the annual economic costs of insufficient sleep in Germany. The estimated amount was calculated by comparing the baseline scenario with three scenarios in which:

- (1) all sleepers with less than seven hours at baseline would sleep seven to nine hours,
- (2) all sleepers with less than six hours at baseline would sleep six to seven hours,
- (3) all sleepers with six to seven hours would sleep seven to nine hours.

For 2015, RAND estimated the annual cost between 1.02-1.56% of GDP, representing around $39.3 to $60 billion USD. This was predicted to increase over time, given a prolonged effect of elevated mortality on labour supply. Thus, in 2030, RAND predicted the economic cost of insufficient sleep to be around 1.21-1.63% of GDP ($46.6 to $69.1 billion USD).

Table 3. Estimated annual cost of insufficient sleep in Germany, relative to the baseline scenario. Source:[51].

Year	**GDP (US$ billions, 2015 prices)**			**GDP (%)**		
Scenarios	1	2	3	1	2	3
2015	60	39.3	54.8	1.56	1.02	1.42
2020	62.3	40.9	56.5	1.61	1.06	1.47
2025	64.7	42.6	58.6	1.68	1.10	1.52
2030	69.1	46.6	62.9	1.79	1.21	1.63

Work absence

Quantifying indirect costs of work absence due to fatigue or sleep disturbances is difficult since physicians rarely document disorders of initiating or maintaining sleep as the reason for employees' sick leave [57, 78]. For instance, among the DAK-insured working population, only 0.29% were documented as unable to work due to a sleep disturbance in 2015, with a comparatively low average of 11 days of sick leave [78]. Taking the roughly 45.27 million working individuals in Germany (2019) [82], this would mean that about 131,000 employees could take sick leave due to a documented sleep disturbance per year. Furthermore, documented sleep disturbances accounted for 0.26% of all absent days from work among DAK-insured employees in 2015 [78]. Considering that there were on average eleven days of sick leave per working individual in 2019 [83], it can thus be calculated that there could annually be around 1.29 million days of sick leave due with sleep disturbances as the documented reason. Organic sleep disorders were reported to result in more sick leave than non-organic sleep disturbances, especially among men. Overall, sleep apnoea accounts for 30% of days of inability to work due to sleep disturbances, and insomnia accounts for 29% [78].

Nevertheless, by comparing sick leave of the German working population suffering from any mental disorder or organic disease with sleep disturbances to those suffering from the same disorders without sleep disturbances, it becomes evident that insufficient sleep can result in substantially longer and more frequent sick leave. In 2017, employed, diseased individuals with an additionally diagnosed sleep disturbance had, on average, 36 days of work absence more than the comparison group (56 days of sick leave in total). Especially employees suffering from mental health disorders (e.g., depression) were comparatively more often and longer unable to work when additionally having difficulties initiating and maintaining sleep [57]. Additionally, the DAK proposed that sick leave due to sleep disturbances has increased significantly from 2.2 absent days per 100 insurance years in 2005 to 3.9 absent days per 100 insurance years in 2015 [78].

Furthermore, even if not documented as the primary reason for sick leave, insufficient sleep largely impacts productivity and ability to work. According to the RAND study [51], around 209,000 working days are lost in Germany per year due to insufficient sleep, equalling more than 1.672 million working hours lost. This working time lost includes absenteeism and presenteeism (i.e., working while sick with reduced productivity).

German employees who are incapable of work receive full salary from their employers for the first six weeks of sick leave. Longer work absence with specified illness is covered by sickness funds with 70% of the last gross salary and a maximum of 90% of the net salary [84]. Consequently, a patient unable to work due to fatigue or sleep disturbance will most likely experience no loss of salary.

7.2.2 Fatigue and sleep disturbances in England

Prevalence of fatigue and sleep disturbances

Although recent concrete numbers are lacking, the prevalence of fatigue [85] and sleep disturbances (i.e., insomnia [86]) in the general British population is commonly noted across scientific literature. Previous research determined an insomnia prevalence of 37% based on self-reported data among 2,192 respondents [87]. In addition, Aviva reported that "to sleep better" was the second most common health ambition after losing weight for adults in the UK in 2016 [88].

Despite the prevalence of fatigue and sleep disturbances in the UK, they often remain unnoticed and/or untreated. For example, a report conducted in 2014 estimated that the number of adults in the United Kingdom who are treated for obstructive sleep apnoea (OSA) was around 330,000, whereas the total population of adults with OSA was estimated to be 1.5 million [89]. Thus, the actual prevalence of fatigue and sleep disturbances in England can be assumed to be much higher.

Direct costs

Total cost of illness

To our knowledge, no estimates of the total cost of fatigue and sleep disturbances to the economy of England exist. A 2013 paper estimated that the total cost of sleep disturbances in 2010 in the UK amounted to €5.63 billion in purchasing power parity [90]. This includes direct healthcare costs and indirect costs associated with sleep disturbances. Information on non-medical costs was not taken into account. Further, a 2017 report suggests that the total cost of Chronic Fatigue Syndrome to the UK is £3.3 billion per year [91]. Given the challenges of diagnosing fatigue and sleep disturbances as laid out in the previous chapter, it is estimated that the actual cost of fatigue and sleep disturbances to the UK economy is much higher.

Diagnostics

According to the year-to-date 2019/20 statistics, 96,685 sleep studies were conducted in the NHS England. A considerable proportion of patients referred to sleep studies (29.5%) had to wait more than six weeks for a test in December 2020 [92]. This could be due to the lack of availability of polysomnography in UK sleep centres. It is estimated that one centre theoretically needs to serve 1.25 million citizens [93]. If paid for privately, diagnostics such as sleep studies can start from £200 [94].

Hospitalisation and inpatient days

According to the Hospital Episode Statistics (HES) for England, there were 32,035 finished consultant episodes with sleep disorders (ICD-10 G47) as the primary diagnosis in English NHS hospitals for 2019-2020. Specifically, there were 30,989 hospital admissions and 1,183 emergency visits with sleep disorders as a primary diagnosis. The average length of stay was one day, resulting in a total of 28,765 Finished Consultant Episodes (FCEs) bed days [95]. For fatigue and malaise (ICD-10 R53) as a primary diagnosis in English NHS hospitals, there were 13,804 admissions in 2020-2021, 12,187 of which were emergency visits. FCEs bed days counted for a total of 29,409. The median length of stay was one day [96]. According to the BBC in reference to the Department of Health of England, the average daily cost of a hospital bed is £400 [97]. This is less than bed costs for inpatient stays across specialties in Scotland, with a mean of £519.38 per unit [98]. Hospital treatment in NHS hospitals is free for people who are ordinarily resident in the UK [99].

Doctor consultations

Fatigue is generally noted to be a common presentation in primary care, also in English settings [100]. A 2016 study found that the average consultation of patients in England with their GP amounts to 10 minutes and 22 seconds [101]. Unit costs in 2019/2020 per hour doctor-patient contact with qualification cost amount to £255 [102], according to the Personal Social Services Research Unit of the University of Kent. Thus, a 10.22-minute-long consultation can be estimated to cost approximately £43.434.

Cognitive-Behavioural Therapy

In the UK, CBT can be prescribed for sleep disturbances such as insomnia (CBT-I) [103]. CBT can be prescribed by GPs. The National Institute for Health and Care Excellence indicates that six 55-minute CBT-I sessions cost £582 in the NHS system [104]. Private sessions cost between £40 and £100 [105].

Pharmacotherapy

The NHS imposes user charges for outpatient prescriptions, currently set at £9.15 per item [106]. However, free prescriptions are dispensed for:

- Over 60 and under 16-year-olds
- 16 to 18-year-olds in full-time education

- Pregnant women or those who had a baby in the previous 12 months with a valid maternity exemption certificate (MatEx)
- Patients with a specified medical condition (MedEx)
- Patients with a continuing physical disability (MedEx)
- Those with a valid war pension exemption certificate and a prescription for the accepted disability [107].

Further, medications prescribed in NHS hospitals are also free of charge for inpatients [106]. Concerning pharmaceuticals for treating sleep disturbances, there were 974,122 melatonin prescriptions dispensed for all medical indications in communities across England in 2018, amounting to around £36 million [108].

Indirect costs

Macro-economic loss

According to the RAND model [51] using mortality and productivity factors in three different scenarios compared to the baseline, the annual economic loss of insufficient sleep in the UK was estimated between 1.36-1.86% of GDP, representing between $43.2 to $50.2 billion USD in 2015. This was expected to increase to 1.63%-2.17% of GDP (between $44.1 to $58.7 billion USD) by 2030.

Table 4. Estimated annual cost of insufficient sleep in the UK, relative to baseline scenario. Source: [51].

Year	GDP (US$ billions, 2015 prices)			GDP (%)		
Scenarios	1	2	3	1	2	3
2015	50.2	36.7	43.2	1.86	1.36	1.60
2020	53.8	40	46.4	1.99	1.48	1.72
2025	57.6	43.3	49.7	2.13	1.60	1.84
2030	58.7	44.1	50.6	2.17	1.63	1.87

Work absence and sick leave

In the UK, the RAND report [51] identified similar amount of working time lost as in Germany. Thus, more than 207,000 working days representing more than 1.657 million working hours are lost due to insufficient sleep. No information on days of sick leave due to sleep disturbances and/or fatigue is available.

7.2.3 Cross-country comparison of direct and indirect costs

The following table presents an overview of direct and indirect socioeconomic costs of fatigue and sleep disturbances in Germany and England presented in this chapter.

Table 5. Quantified direct and indirect costs of fatigue and sleep disturbances in Germany and England.

	Cost	Country	Value
Direct costs	Cost of illness (healthcare resource consumption)	DE	€1.03 billion (ICD10-F41 and ICD10-G47 in 2015)
		GB	€5630 million purchasing power parity (sleep disturbances in 2010); £3.3 billion (per year; chronic fatigue syndrome)
	Hospitalisation and inpatient days	DE	104,659 cases of hospitalisation (ICD10-G47) resulting in 205,721 inpatient days in 2018
		GB-ENG	32,035 finished consultant episodes (ICD10-G47 as primary diagnosis) in England in 2019/20
	Costs of inpatient care for patient	DE	€20 taking the average of 2 inpatient days
		GB-ENG	£0
	Drug bill for patients	DE	€5-10 per outpatient prescription
		GB-ENG	£9.15 outpatient prescription charge per item
	Doctor consultations	DE	€31.78 - 42.45 per 10-minute consultation
		GB-ENG	£43.434 per 10.33-minute consultation
	Cognitive-behavioural therapy	DE	SHI patients: no OOP, payers reimburse therapists €86,90 per one-hour session OOP for private patients: €50-150/session
		GB-ENG	£582 for six 55-minute sessions with NHS providers (no costs for the patient) £40-100 for private sessions
	Diagnostics	DE	Costs for statutory health insurances: €500 per night spent in sleep laboratories 104,327 inpatient polysomnographies (2019) 61,912 inpatient cardiorespiratory polygraphies (2019) 4,536 inpatient MSLT/MWT tests (2019)
		GB-ENG	96,685 sleep studies (NHS England YTD 2019/20), costs unclear.
Indirect costs	Annual macro-economic loss (morbidity, loss in productivity at work and school)	DE	$60 billion USD (1.56% of GDP in 2015)
		GB	$50.2 billion USD (1.86% of GDP in 2015)
	Working time lost due to absenteeism and presenteeism	DE	209,024 working days and 1,672,192 working hours lost
		GB	207,224 working days and 1,657,792 working hours lost
	Days of sick leave	DE	Total of 1.29 million days of sick leave per year with sleep disturbances as the documented reason
		GB	No information available

7.3 Preliminary impact indicators

An essential step in a socioeconomic evaluation framework is to model impact indicators of increasing specificity for the selection of defined measurable outcomes which serve as representations of benefits and costs. Through the present framework development process, these preliminary indicators were based upon desk research, as well as work done for related deliverables by the consortium. Discussions between participants of workshops related to these deliverables as well those on stakeholder engagement within the wider consortium informed our initial findings. It is expected that the implementation of digital endpoints can contribute to the digitalisation of clinical trials as well as allow for improved health outcomes and decreased healthcare resource utilisation in clinical care, all of which in turn, result in resource liberation and cost savings.

Based on the initial findings, the table below shows preliminary impact indicators for selected stakeholders. Impact indicators here refer to a functional collection of benefits and costs through which measurable outcomes can subsequently be developed. In addition to patients, healthcare providers and health and social care payers, national competent authorities responsible for regulating and approving medical devices are considered. Healthcare professionals were aggregated with healthcare providers as a stakeholder group due to the overlap in their benefits and costs as were the pharmaceutical and medical devices industries. These preliminary impact indicators will be reviewed in close exchange with involved stakeholders and adapted as the empirical work develops. Data collection will incorporate findings from primary sources, which in our case refers to the direct involvement of stakeholders through guided workshops, expert interviews, and semi-structured questionnaires.

Table 6. Preliminary impact indicators as benefits and costs of the implementation of digital endpoints

Stakeholder	Benefits	Costs
Patients	• Earlier and more personalised interventions with a better understanding of the relationship between health, disease and fatigue/sleep disturbance • Decreased pain sensitivity, disease activity, co-morbidity and mortality risk due to improved sleep patterns, overall better physical and mental health • Patient safety due to appropriate pharmacotherapy and lower risk of accidents (e.g., falls, work accidents, road safety) • Patient empowerment, self-efficacy, engagement, disease self-management, patient-centric endpoints • Increased social functioning • Higher productivity and cognitive performance • Decreased absenteeism and presenteeism • Cost savings from fewer prescriptions or unnecessary hospitalisation due to tailored therapeutic interventions	• Skills development and training costs • Adaptation time and inconvenience related to digital device usage

Stakeholder	Benefits	Costs
	• Time saved from fewer doctor consultations as a result of remote monitoring and better health • Sleep monitoring in home settings for extended periods of time with reduced burden for patients; fewer diagnostic tests • Increased QoL, HRQoL and ability to execute ADLs	
Patient organisations	• Provision of increased services for patients • Increased networking with other organisations and opportunities to collaborate • Enhanced health and disease knowledge, complete picture of burden	• Skills development and training costs • Costs associated with patient outreach, patient recruitment for clinical trials, and for dissemination of new findings.
Healthcare professionals and providers	• Real-time monitoring, improved patient risk stratification, diagnostic management, and automated decision-making support due to continuous, objective, precise patient data • Enhanced health and disease knowledge, complete picture of burden • Healthcare resource liberation (fewer hospital admissions, inpatient days, consultations, diagnostic tests) • Improved assessment of treatment effects • Time saved from automated monitoring and data reporting • Easier communication and information-sharing in multidisciplinary care team (GPs, hospital staff, sleep specialists, mental health professionals) • Improved patient-provider communication	• Training, skills development, and time spent for using devices and obtained data • Costs associated with technical implementation of tools and data platform • Forgone income from avoided consultations, hospitalisation, and diagnostics
Payers / third-party insurers and purchasers	• Generation of data for deciding on reimbursement policies and billing, preventing delays in decisions and patients' access to new therapy • Cost savings from lower intervention costs, diagnostic tests and overall healthcare utilisation • Cost savings related to improved disease management and decreased co-morbidity	• Reimbursements for therapeutic interventions and approved devices

Stakeholder	Benefits	Costs
National competent authorities	• Access to high-density, accurate, objective and reliable trial data and transparent information for rapid assessment and scientific evaluation of medical device • Efficient pre- and post-market surveillance • Promotion of digital health technologies • Potentially shorter clinical trials with fewer subjects needed for recruitment in the future • Access to high-density, accurate and reliable data on effectiveness, cost-effectiveness, benefits and harms of health technology • Market authorisation studies meaningful for HTA • Efficient pre- and post-market surveillance • Promotion of digital health technologies • Data for evidence-based reimbursement and pricing decision-making	• Administrative costs of authorisation procedure
Pharmaceutical, health-IT and medical devices industries	• Reduce operating costs (ex: setting up physical clinical trials) • Increase recruitment rates and inclusive diversity in trials • Accelerate drug discovery and development of new therapies • Create patient-centric approaches • Reduce participation burden • Accurate information on how therapy affects the disease • Opportunity to collaborate	• Costs of provision of devices • Security risk on collected participants' data • Data platforms, data analytics • Greater personnel needed to support patient's questionnaires and concerns.
Research community	• Enhanced health and disease knowledge • Opportunity to collaborate • Increase recruitment rates and inclusive diversity in trials • Access to high-density, accurate, objective and reliable trial data and transparent information for scientific evaluation	• Security risk on collected participants' data • Data platforms, data analytics • Greater personnel needed to support patient's questionnaires and concerns.

8 Exploitation and sustainability framework

In accordance with IMI's strategic vision to accelerate research and development in Europe's biopharmaceutical and healthcare sectors [109], it is intended that the exploitation and sustainability of IDEA-FAST will be strengthened by leveraging synergies across consortium partners. As such, the exploitation and sustainability framework was developed with a focus on fostering engagement with partners in all work packages. The framework is envisioned to be adaptable to evolving developments in the project, thereby supporting the utilisation of project results beyond the completion of IDEA-FAST. Highlighted as being critical to the sustainability and success of the project is finding resources that allow developed assets to be integrated into the wider global network of organisations, researchers and healthcare professionals working on fatigue and sleep disturbances.

The current chapter defines the exploitation and sustainability framework for IDEA-FAST by specifying the initial steps undertaken. These include the formation of the Exploitation and Impact Sub-committee (EIS), a first identification of key exploitable assets, delineation of value propositions, description of data sharing and intellectual property rights concerns, development of user scenarios, and the drafting of a sustainability strategy.

8.1 Establishing the Exploitation and Impact Sub-committee

As part of the exploitation and sustainability planning, the EIS was established. The EIS is an interdisciplinary sustainability advisory group that is coordinating oversight of issues pertaining to key exploitable assets and other major project outputs, intellectual property, data use, regulatory strategies, sustainability models and other business matters, consisting of WP Co-leads and designated experts. The first meeting of EIS explored the consortium's shared understanding of sustainability and exploitation within IDEA-FAST, identification of key exploitable assets, and exploration of issues that the consortium might need to face toward achieving sustainability of the project outputs (Appendix A – EIS Jamboard session). The EIS is further set to meet during the project according to important milestones and current project progress.

8.2 Identifying key exploitable assets

IDEA-FAST aims to develop various assets within the health technology domain that are expected to mature over the course of the project. Assets may refer to products, prototypes, services, methodologies, guidelines, tools, procedures, components, know-how, software, apps, platforms, algorithms, and publications etc. all of which can benefit different stakeholders. A classification system for the assets within IDEA-FAST was adapted from the IMI Field Manual: Scaling innovations emerging from public-private partnerships [110], wherein assets are categorised as:

- Products: An article or substance that is manufactured or refined, or a service that is offered
- Knowledge resources: Findings, insights or skills acquired through technical or process innovation
- Collaborations: Networks for exchanges of information, services, or goods between organisations to create synergies

However, it is important to note that different types of assets require different viability roadmaps and business models. As such, elicitation and modelling of exploitable assets is seen as an iterative process, to be performed several times over the project lifetime as assets mature. Within the first reporting period, key exploitable assets were identified by surveying all consortium partners (see Appendix B),

including several follow-up and feedback sessions. Responses were comprehensively tabulated (see Appendix C) and selected results are presented below.

8.2.1 Products

Some of the key products envisioned to be developed within IDEA-FAST are:

- Digital endpoints to assess fatigue and sleep disturbances, and other ADL/HRQoL for patients with IBD, RA, SLE, PSS, PD and HD
- Data management platform to support data acquisition, integration, storage, and analysis, which will include data standards, clinical and digital datasets, and an analytic environment with customised scripts.
- Data analysis software package
- AI Toolbox for robust multi-variate time-series analysis
- IDEA-FAST Biobank

Digital endpoints for fatigue and sleep disturbances and other ADL/HRQoL

Within the lifetime of IDEA-FAST, the primary objective is to identify digital biomarkers and corresponding technologies for the evaluation of fatigue and sleep disturbances. This includes clinical validation, and as a secondary objective, exploration of digital correlates of other ADLs developed through profiling activity-related, biological, neurocognitive, and behavioural factors in patients with IBD, RA, SLE, PSS, PD and HD. The overall vision of the project is to develop validated disease agnostic digital endpoints that can be used in clinical, interventional, and observational studies, thereby supporting advances in clinical care pathways, drug development, and patient-self-management.

Data management platform

To allow for large-scale data acquisition, integration, storage, and analysis a data management platform (DMP) is currently being developed (Figure 6) within the project. The IDEA-FAST DMP will serve as a shared work environment for curated harmonised data related to fatigue and sleep disturbances. Clinical and device data are captured and transferred to the DMP via secure APIs and the datasets generated within IDEA-FAST will be both standardised and compliant with GDPR. The DMP will contain an analytic environment that can support various tools, including a data analysis pipeline and customised scripts with the incorporation of an AI Toolbox for robust multi-variate time-series analysis. Further specifications are presented in D5.2.

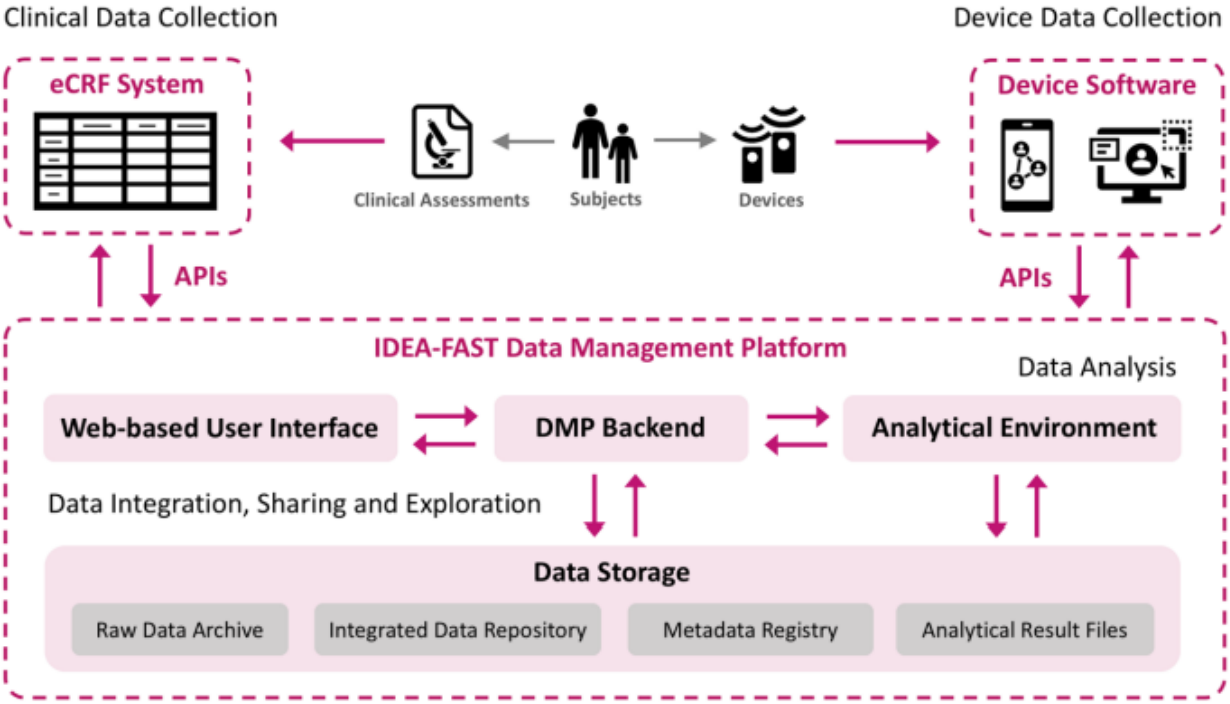


Figure 6. Components of the IDEA-FAST data management platform and data flow. Source: D5.2 Data management platform specification[111].

Data analytics software package

A data analytics software package that includes steps such as validation, feature extraction, data visualisation and further analysis is also being developed. It is described in D5.1 as follows "The data analysis steps form a modular pipeline, generating intermediate and final output files from different processing steps. These intermediate files are in an open and fully documented format allowing the community to further use the results for additional research purposes. The routines for reading and writing the intermediate files will be fully documented and available with (Python) source code" [112]. The data analysis pipeline will be further integrated into the DMP analytical environment [28].

AI Toolbox for robust multi-variate time-series analysis

An AI Toolbox for multi-variate time-series analysis will be developed, including AI methods for:

- Handling of poor-quality signals
- Earning personal activity patterns
- Robust ML approaches for weakly annotated data
- Multimodal data aggregation and visualisation of heterogeneous data sources
- Handling multi-variate, weakly annotated time-series analysis of personal data
- Time-series data related with not completely reliable ground truth (PROs)

ML/AI approaches are useful tools for transforming raw signals into actionable information and combinatory algorithms will be developed to accommodate different sensing modalities. The purpose of the proposed algorithms is to improve the identification of some elements of the patient's state of health (quality of sleep, fatigue, etc.), starting from the data acquired by the devices. Improving these

algorithms can result in more accurate monitoring of the evolution of the patient's state of health. The AI toolbox plays a key role in mapping the information collected from the digital devices to PROs.

IDEA-FAST Biobank

During the FS and the COS, a biobank containing blood, urine and stool samples will be established. This will consist of samples from six patient cohorts, i.e., from 17 centres across ten countries within Europe, representing geographic, ethnic and healthcare-system diversity. In accordance with ethical guidelines of informed consent and participatory design, it will be made clear to participants that the donation of their biological samples is voluntary and will not affect their eligibility to take part in the study. Samples access will be governed by standardised application procedures with all applications being reviewed by the IDEA-FAST steering committee.

8.2.2 Knowledge

Assets categorised as knowledge are concretised as scientific articles, presentations, or reports within the project. These can be exploited in future studies by the wider network of organisations working on contexts similar to IDEA-FAST and include:

- Results and analysis of the FS and COS, such as knowledge on the acceptability of selected devices, knowledge on the design and use of visualisation for participants, knowledge regarding recruitment of patients, and related publications
- Training materials and trial protocols from the FS and COS
- Knowledge regarding the ethical approval process of the COS
- Knowledge of regulator, HTA, and payer requirements for digital endpoints
- Cross-industry/academic pre-competitive alignment
- Knowledge of involving and engaging patient groups across research cycles

The results of the feasibility study demonstrate the extent to which digital devices and PROs can be simultaneously assessed, i.e., in parallel, without excessively burdening patients. The study shows the suitability of devices for various patient groups, including those with different diseases. Additionally, it provides a good estimate of the expected levels of data quality and completeness within a wearable devices context thereby facilitating calculations of required sample sizes in future studies. Lessons learnt from this study (e.g., level and extent of patient support material and training of staff) will help to create targeted supportive material for patients and study staff which can help improve the quality of data captured in future studies and have an impact on future patient recruitment strategies.

The COS study aims to identify digital outcomes that may serve as clinical endpoints, whereupon they can be used during drug development as validated endpoints to assess fatigue and sleep disturbances. As fatigue and sleep disturbances are disease-spanning critical problems for many patients it is essential to have these validated clinical endpoints accepted by EMA. Qualitative advice on evidence standards necessary for regulatory approval will be built into the COS design as far as feasible and would help pave the way toward regulatory acceptability of one or several digital endpoints. As official guidance on regulatory approval requirements for digital endpoints are not yet provided by EMA, HTA bodies or Payers, the IDEA-FAST project is developing an understanding of the requirements and gaps in current guidance. This knowledge will further inform future researchers on the development and validation of digital endpoints in related contexts.

Patient involvement and engagement within IDEA-FAST is considered throughout the project. The patient engagement strategy in IDEA-FAST follows four aspects: Co-design, Involve, Consult, and Inform. This ensures that patient representatives are given an active, decision-making role as co-researchers in some areas and are able to provide feedback and advice in other areas. Furthermore, they are also kept informed about priorities, activities, outcomes & impacts. The knowledge and methodologies generated within the Patient Involvement and Engagement Group will be of benefit for future projects.

Overall, knowledge resources generated through the project, e.g., publications, also exemplify the benefits of public-private collaborations, i.e., cross-industry/academic pre-competitive alignment, to tackle the challenges of complex problems in healthcare such as those presented by fatigue and sleep disturbances. These knowledge resources raise the public profile of the burden of fatigue and sleep disturbances and contribute to increased public awareness of their impact on quality of life.

8.2.3 Collaborations

Collaborations are characterised as networking-based programs or initiatives that aim to connect stakeholders better and promote the exchange of information, services, or goods across the wider community of organisations working on a project´s topic or domain area. They contribute to a project's scalability by facilitating the participation of multiple initiatives, consequently recruiting new users and allowing the application of project outcomes to new areas. Within IDEA-FAST's context of fatigue and sleep disturbances, the following initiatives were identified as exploitable collaborations:

- Digital Health Catalyst (DHC), a platform for early career researchers (ECRs) co-developed by IDEA-FAST and Mobilise-D
- The Neuronet platform for the integration of IMI projects related to neurodegenerative disorders
- The VOICE platform for patient engagement and outreach

Digital Health Catalyst

IDEA-FAST and Mobilise-D, which are both funded under the IMI JU2 initiative, are collaborating to establish the DHC. In the first instance, the DHC will be a platform that will support early career researchers (ECRs) across both academia and industry to develop health related digital technologies. Additionally, the DHC is seen as an excellent vehicle for sustainability and as such the scope of its function is likely to expand into areas such as technology development, setting research agendas and promoting translation of research into clinical practice.

The Digital Health Catalyst recognises that the work of the consortium provides a platform for ECRs (Fellows & PhD students) to grow professionally, expand their vision, enhance multi-disciplinary understanding and in turn support their future careers. It will develop and deliver a programme of activities to ensure that ECRs have wide exposure to the rich scientific environment in the consortium within and across the partners; and will help to provide training, help ECRs to publish their work, help to design new research projects, provide access to project data, and create networking opportunities. By doing so, the DHC hopes to help build the next generation of leaders in Mobility, Fatigue and Sleep research. By expanding the horizons of our Fellows and PhD students, the catalyst hopes to contribute to faster and better research in the next decade. Once established, the DHC will also reach out to other relevant IMI projects for potential inclusion.

Neuronet

Neuronet is an IMI-funded initiative aiming to support and better integrate projects related to neurodegenerative disorders across the IMI domain. One of its objectives is to create an overall platform for efficient collaboration, communication, and operational synergies among present and future IMI projects working on neurodegenerative diseases. IDEA-FAST is participating in specific Neuronet working groups on issues related to data sharing, regulatory interactions and digital endpoints and disseminating public deliverables across the Neuronet knowledge platform [113].

Patient engagement through the VOICE platform

The VOICE Platform [114] is a community comprising large networks of patients, carers and members of the public involved in all stages of research cycle with research communities and industry. VOICE supports researchers to conduct meaningful patient and public involvement, where members contribute insights, experience, ideas, and vision to identify unmet needs and opportunities, to drive innovation and improve health research. The IDEA-FAST project will conduct certain patient engagement and involvement activities through the VOICE platform, thereby contributing knowledge and strengthening public engagement in research.

8.3 Eliciting value propositions

A value proposition is a clear statement of how a proposed implementation relates to some improvement for the user, what specific benefits it brings, and how it differentiates from others. It sets out and describes how the proposed implementation addresses an unmet need [115]. To understand how different stakeholders might benefit from the assets produced in the project, questions on foreseen value propositions were included as part of the initial identification of exploitable assets (see Annex A and D).

Summarily, input from partners on value propositions asserted that digital biomarkers would improve treatments for fatigue and sleep disturbances, provide new clinical endpoints for the pharmaceutical industry for clinical trials, serve as candidates for regulatory acceptance of digital endpoints, and improve patient self-management. The AI toolbox would improve identification of patients' state of health (quality of sleep, fatigue, etc.), transforming raw signals from devices into actionable information; and with further algorithmic development resulting in more accurate monitoring of the evolution of patients' health status. Integration of the AI toolbox and other data analytic pipelines into the envisioned data management platform would be of value to various research projects, both industry- and academia- driven, involving healthcare data curation and especially those involving wearable digital devices.

As part of the exploitation and sustainability framework it is envisioned that detailed value propositions on selected exploitable assets, such as the data management platform, AI toolbox, and digital endpoints, will be conducted at subsequent stages of the project using a canvasing methodology as presented in the figure below.

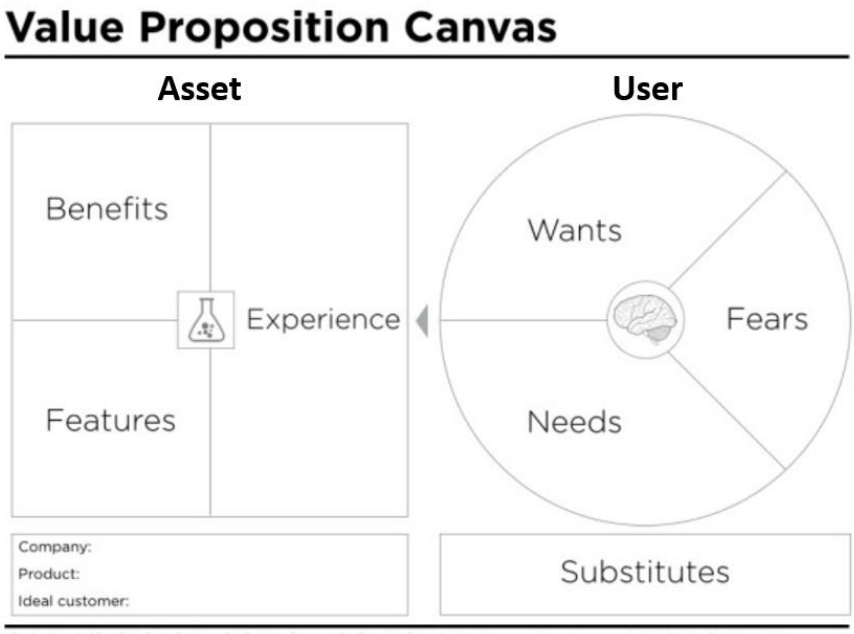


Figure 7. Value proposition canvas

8.4 Delineating guidelines on use of data and intellectual property rights

Following identification of exploitable assets and their value propositions, the next step entails delineation of the Intellectual Property Rights (IPR) management and data usage rights for assets. In order to define IP rights for each recognised asset, partners will be required to provide input in an updated exploitable assets table (Appendix C). In case of joint ownership of assets, management of exploitation activities will be addressed and will examine the terms under which the results can be exploited outside the project, including a discussion of IPR risks proposed and mitigation strategies. Specific IPR concerns, such as confidentiality, ownership of assets, access rights, and related obligations, will all be discussed with partners during planned exploitation workshops and incorporated into corresponding questionnaires. Major issues concerning IPR are to be handled procedurally as defined in the Consortium Agreement. Results of discussions on jointly owned intellectual property will be included in D9.4.

Data management specifications are highlighted in D5.1 [116]. The IDEA-FAST data management platform is envisaged as a web-based user interface with secure access control that allows researchers to analyse pseudonymised data. It will be a key principle that no data, internal or external, will be available to anyone without full ethical approval, and that only pseudonymised data would be shared within the Consortium. The project's GitHub repository will host technical documentation and a user manual for the DMP, as well as the source code for all software generated throughout the project. Two-factor authentication will be used to gate access rights for the platform. Extant datasets will be transferred to the platform, and their use will be governed by data sharing agreements between the contributor and the consortium. Additionally, it is important to note that IDEA-FAST the consortium has decided to opt out of the "Open Access to Data Pilot for IMI projects (no applicability of Art 29.3 of the Grant Agreement)," hence there will be no requirement for immediate open access to data. Nevertheless, it is intended to allow access (via the DMP) to the data generated by the project once the project has been completed.

Over the course of the project, the IDEA-FAST Steering Committee is responsible for selecting which data subsets will be designated as open or limited access, determining their access conditions including

licensing fees. The complete governance structure of IDEA-FAST datasets beyond the lifetime of the project will be detailed as part of the final Sustainability and Exploitation Plan.

For the datasets generated as part of the IDEA-FAST project, it falls under the purview of WP8 to synchronise data use and data sharing guidelines with current ethical and legal frameworks for data protection. Informed consent forms will be designed to ensure that the participants in the IDEA-FAST clinical studies are given clear information about the project strategy for data storage, sharing and reuse, including the potential for their pseudonymised data to be shared with countries with data protection legislation different from the EU [117].

8.5 Creating user scenarios for implementation of digital endpoints

Within the framework, user scenarios were created to illustrate situations in which an end-user would interact with the to-be-developed-system. As digital endpoints for fatigue and sleep disturbances are yet to be implemented, the scenarios support envisioning future process pathways. Four scenarios were selected to depict how the envisioned implementation of digital endpoints would potentially affect researchers, clinicians, and patients, as described in sections 8.5.1 and 8.5.2, below.

8.5.1 Clinical research

As-is situation

Whereas the COVID-19 pandemic has accelerated the shift from fully centralised to hybrid and decentralised trials, most current clinical trials are utilising centralised approaches, therefore not fully harnessing the potential of digital technologies, including digital endpoints. Patients need to present themselves to testing clinics, stay there overnight or for several days, which can be an additional stressor and may provide inaccurate measurements. Moreover, current clinical research relies on PROs described in chapter 4.2, thus lacking additional objective measurements. Therefore, essential data that could aid the identification and treatment of fatigue and sleep disturbances in various patient populations is not collected.

To-be situation

Decentralised observational and experimental clinical trials are supported and increasingly conducted following the approval of the digital endpoints to measure fatigue and sleep disturbances developed in IDEA-FAST. Their success has encouraged increasing support mechanisms around digital devices for the use in decentralised trials. Moreover, the independent validation of the digital endpoints developed in IDEA-FAST encourage pharmaceutical companies of all sizes to utilise them in clinical trials as they can reap the benefits without high initial investments in the development of their own digital endpoints. As the endpoints are disease-agnostic, a variety of patient populations benefit from the multitude of clinical trials conducted. In a decentralised clinical trial utilising the endpoints, patients receive devices and are monitored at home to capture cognitive, physiological, and behavioural data via wearables, apps, and other devices. Data is safely transmitted to the data management platform. At the beginning of each trial, healthcare professionals (i.e., nurses) visit each patient and explain how to use the devices. They further visit the patient at the end of the trial to collect the devices so that they can be re-used. Further household visits might be scheduled, and informal carers can be involved depending on the clinical trial. Due to the lesser impact of the clinical trial on the patient's daily life, given that they can stay at home, attrition rates are lowered, and easier patient recruitment is enabled.

Through the digital endpoints and use of digital devices, researchers can closely monitor the study participants, collect objective data that patient-reported outcomes cannot provide, measure the efficacy of new drugs more quickly, accelerate clinical trials, and gather data necessary to end a clinical trial

more quickly if there are indications that the drug studied is ineffective, thus allowing for the re-allocation of funding to more promising drugs.

8.5.2 Clinical care

NDD Scenario for fatigue

As-is situation

Mary is a 76-year-old woman living with PD. She frequently experiences tremors, has difficulties with her balance and rigidity. In addition, Mary also has depression, for which she infrequently talks to a therapist. To improve and maintain functional ability and alleviate difficulties with balance, she receives regular physiotherapy. She is prescribed carbidopa-levodopa to manage PD and citalopram for depression management.

Recently, Mary's symptoms have been getting worse. Additionally, she has been reporting extremely low energy levels to her GP in routine appointments. She explains that, although she sleeps a lot, she constantly feels "really tired." As a result, she has very little energy to spend time with her family and friends, making her feel lonely and frustrated. Her social care and support service is trying to help her with day-to-day tasks, but Mary states that she misses spending quality time with her family and friends.

Initially suspecting a relation to depression, Mary's GP refers her to her psychiatrist. Her psychiatrist sent her back home, stating that feeling exhausted is just a normal part of getting older and chronic disease. Mary feels misunderstood and, although she starts to doubt herself, she decides to raise the topic of low levels of energy again at her next routine GP visit. Her GP considers that Mary's tiredness could also be daytime sleepiness related to her medication and consequently suggests that her drug and dosage schedule should be reviewed and adapted by a PD specialist. She follows this advice, consults her specialist, and adheres to the adapted treatment. Her low levels of energy, however, prevail. At this point, Mary wants to give up as she feels very discouraged from being sent from one health care professional to another without receiving any of the answers she seeks. However, her social carers motivate her to consult her GP again

Finally, Mary's GP recognises that she is fatigued. Mary and her GP review her day-to-day activities and sleep behaviour to evaluate what could alleviate her fatigue. As a result, they establish action points and routines that Mary can follow to help her stay active during the day and maintain a proper sleeping rhythm. This enables her to manage her fatigue slightly, but the cause(s) remain(s) unclear.

To-be situation

With the adoption of digital endpoints and solutions to assess fatigue, Mary's healthcare professionals started managing fatigue differently. Mary began to regularly fill out a short fatigue questionnaire specific to Parkinson's disease patients with the help of an informal carer and use digital devices that collect data on her health status. She and a family member assisting her then discuss the results with her healthcare professionals, who try to identify when and how her fatigue occurs and which aspects of daily life it is connected to whilst altering her treatment to alleviate associated symptoms. Although she was initially reluctant to use digital solutions, she appreciates that she can learn more about her fatigue, how to manage it and that the monitoring data / composite digital endpoints enable a productive conversation even with healthcare professionals who previously discounted her experiences with fatigue. With all this information, Mary's doctors were able to adapt her treatment to lessen its impact on her daily life. Thus, she could focus on coping better with her symptoms associated with Parkinson's disease and spend more time with her family and friends when she has the energy to do so.

NDD Scenario for sleep disturbances

As-is situation

Leo is a 68-year-old man with Parkinson's disease. It was only recently diagnosed. Leo experiences a slight tremor in his hand, for which he is prescribed a dopamine agonist. He states that the most debilitating symptom he experiences in relation to Parkinson's disease is the insomnia and REM sleep behaviour disorder (RBD) he has been suffering from for a few months. Due to this issue, he feels like he is never fully rested and cannot follow his previous daily routine. In addition, he has issues connecting with his partner, with whom he shares a bed, as he frequently wakes them up with the movements and sounds that he makes.

When he mentioned this to his GP at a routine appointment, she explains that sleep disturbances like the ones he describes are frequently associated with Parkinson's disease. She refers him to a sleep clinic to assess this issue further. Leo has to ask a friend to drive him to the sleep clinic, which is almost 1 hour away from where he lives. Although Leo appreciates the opportunity to find better ways to deal with his sleep disorder as a result of the data collected at the sleep clinic, he finds it a hassle to go there as it is so far away, and he must make the trip multiple times.

To-be situation

With the introduction of digital endpoints to measure sleep disturbances, Leo's GP offers him the chance to take home devices that assess his sleep from the comfort of his own home. He took up the offer as he felt very stressed by having to go to the sleep clinic. As the tremors Leo has been experiencing have been getting worse, he requires the help of his partner to put on the devices. Leo and his partner receive detailed instructions on how to do that from Leo's GP. Whereas it is difficult for them the first few times, it quickly becomes a routine. With the data gathered during the assessments conducted with the devices, Leo's GP adapts his treatment, resulting in better sleep.

IBD scenario for fatigue

As-is situation

John is a 40-year-old man with Ulcerative Colitis (UC). His symptoms have typically included persistent diarrhoea, abdominal pain, and rectal bleeding. He has been prescribed a regiment of 5-aminosalicylates, corticosteroids, and immunomodulators as treatment for his UC.

Over the last six months John has had no energy to complete many of his day-to-day tasks. He is constantly exhausted and describes himself as having 20% energy on some days and 50% on others. He has difficulty concentrating and complains of a 'mental fog' that leaves him unable to think properly. These symptoms have greatly impacted John´s quality of daily life. He is unable to focus on his work or socialise and some of his friends have even called him lazy. John states that he is 'able to manage the frequent trips to the bathroom due to his disease, but this constant exhaustion is killing him.'

John has visited his GP several times for help with his exhaustion. Initially, his GP first told him that his energy levels would be better once the medications start working and was then told that feeling tired was a normal part of everyday life and that John should focus on resting more and getting better sleep. When John's complaints persisted, the GP once again recommended that John improves his sleeping habits and worked with him to develop an improved sleep hygiene plan. Seeing no improvement, John's GP referred him to a sleep clinic, however they were unable to help him. Finally, John consulted his IBD specialist regarding exhaustion, a symptom he had not discussed in the IBD clinic before.

The IBD specialist was able to recognise John's continued symptoms as fatigue and tested for anaemia, inflammatory markers, and various vitamin and mineral deficiencies. Being unable to pinpoint a cause

for John's fatigue, John was then referred to a psychiatrist for potential depression and told by the IBD specialist that there was nothing wrong with him and that he would have to just manage as best as he can.

John's situation continued as such with no relief from his exhaustion for over two years. Following current research to develop digital endpoints for fatigue and sleep disturbances, one day John received a call from his IBD specialist.

To-be situation

The IBD specialist explained to John that new advances in the integration of multimodal (different types of) data has led to the development of so-called digital endpoints for fatigue and sleep disturbances (characteristics that using digital solutions and devices measure how a patient feels and functions) and that their use may be helpful for managing UC and other IBD related symptoms.

The specialist recommended that John use a new fatigue-related digital app in the two weeks before his next appointment. The app digitally incorporated validated questionnaires on fatigue with John´s electronic patient record and assessed John's fatigue from multiple perspectives including its effects on John´s physical, emotional, and social health. At John's next appointment, he was prescribed new wearable technologies to better monitor his fatigue. Through the combined use of wearable technology and the associated fatigue app, John's clinicians were able to monitor his fatigue and changes in fatigue over time. This enabled John to have an interdisciplinary clinical team around him who had access to his fatigue data.

This in itself was a huge relief to John because for the first time his symptoms were being addressed appropriately. With the data, John's treatments were modified to be more specific to him, taking his needs and goals into account. John's symptoms were taken more seriously by his GP, and during periods of increased levels of fatigue, they were together able to prioritise where to spend energy, allowing for better management of the disease. By being better able to track his fatigue levels with the endpoints, John was able to incorporate exercise once again into his life which in turn led to an improvement in his symptoms. His clinicians were also able to repeatedly test for signs of inflammation, guided by the data points available. Over time, the perspective of John's GP on the impact of fatigue on patients changed significantly and John's data even helped his GP to better understand the mechanisms underlying fatigue.

By having the data to correlate fatigue levels to his daily activities, John was able to better predict his fatigue and schedule breaks to recover accordingly. With his symptoms being appropriately recognised and the profile of fatigue being raised internationally through the implementation of digital endpoints, John was also able to join more fatigue focused patient support groups, expanding his social support and accessing further resources. When asked about his experience again, John thinks back to that one phone call, and fondly highlights it as ''the call that saved my life''.

8.6 Towards a sustainability strategy

IDEA-FAST's sustainability strategy is informed by the high potential that the project's results hold for furthering the validity and acceptability of digital endpoints across their various use cases. One of the main challenges of the project and its clinical studies is connecting sustainability to the exploitation of developed assets, owing to the still-early maturity level of the envisioned digital endpoints for fatigue and sleep disturbances and their lack of regulatory approval. Nevertheless, finding mechanisms for maximising impact is a key focus for the proposed sustainability strategy plan which includes the following:

Business modelling and SWOT analysis

Business modelling of exploitable assets is central to a well-developed sustainability strategy. Within the IDEA-FAST context, we plan to identify key innovations from the wider set of all exploitable assets that can serve as products which could be taken to market. The business modelling includes defining the product's functionality, targeted user-base, value proposition, competitive advantage, and business case. To create the business case, a SWOT analysis for selected assets is to be applied, whereby a product or organisation's strengths, weaknesses, opportunities for and threats to commercialisation will are identified. The analysis will support development of business models and strategies that leverage strengths to overcome weaknesses and threats allowing for the translation of results into marketable implementable assets cross-referenced to the project's specific objectives.

Analysis of public-private partnerships

Public-private partnerships (PPPs) are commonly defined as mutually beneficial collaborations between the public sector and a group of prospective private collaborators. When people talk about the advantages of PPPs, they usually bring up a slew of economic and social objectives, the most important of which is increased efficiency and effectiveness [118]. The sustainability strategy for IDEA-FAST will incorporate an analysis of PPPs which necessitates a thorough examination of existing models as well as any relevant innovative partnership models in the healthcare sector that are relevant to the project. This entails looking into shared ownership, organisational models, codes of behaviour, policies, and workflows that can be used. Sister initiatives that can offer beneficial paradigms and potential partnership prospects would be given special consideration through identification of already existing infrastructures and funding opportunities etc.

Integrating policy considerations

Policy considerations are a vital component of a well-defined sustainability strategy. Here we refer to integrated policy considerations as encompassing both horizontal sectoral integration (between different departments and/or professions in public authority) and vertical inter-governmental integration in policymaking (between different tiers of government). Comprehensiveness (recognising a broader scope of policy consequences in terms of time, space, actors, and issues), aggregation (a minimum extent to which policy alternatives are evaluated from an 'overall' perspective), and consistency (a minimal extent to which a policy penetrates all policy levels and all government agencies) can be considered basic requirements for policies to be classified as 'integrated' appropriately within a defined context [119]. Within the IDEA-FAST context these policy considerations apply to regulations concerning digital endpoints as well as those on the governance and execution of the clinical studies. Additionally, regulations considering data usage in the EU including health data usage must inform governance and structure of the IDEA-FAST DMP.

Cataloguing challenges towards sustainability

Many potential technical advancements in health and social care are marred by individual non-adoption or abandonment, as well as failed attempts to scale up locally, disseminate across geographic areas, or sustain the innovation over time at the organisational or system level [120]. Barriers and facilitators are frequently used to explain why technical advancements are not adopted. For example, technology barriers, patient barriers, staff barriers, team barriers, commercial and financial barriers, and governance and regulatory impediments were all noted in a recent assessment of telemedicine in heart failure [121].

The IDEA-FAST sustainability strategy will therefore catalogue identified challenges towards sustainability of the project´s assets. An initial Jamboard exercise was conducted to begin this process (Appendix B) where members of the EIS committee were asked to first present what they understood by exploitation and sustainability followed by identification of issues towards sustainability and

exploitation of the project´s assets. A key concern highlighted during this session was that IDEA-FAST would not be sufficient for the regulatory approval of developed digital endpoints because such regulatory qualification requires an interventional clinical trial as evidence. As such, plans for the sustainability of the digital endpoints must include an interventional clinical trial to fulfil this obligation, perhaps through another project or a PPP with a pharmaceutical industry partner. These issues and more inform the process of moving towards a comprehensive sustainability strategy for IDEA-FAST.

9 References

1. Ramasastry, R., et al. *D3.5 First version of guidance on sustainability*. 2020. NEURONET. Availablec from: https://www.imi-neuronet.org/wp-content/uploads/2020/06/NEURONET_D3.5_SUSTAINABILITY_Final.pdf
2. European Commission (EC), Directorate-General Education and Culture. *Sustainability of international cooperation projects in the field of higher education and vocational training: handbook on sustainability. 2006 Publications Office*, 2007 Available from: https://op.europa.eu/en/publication-detail/-/publication/6647795f-b5d3-4cae-9b9c-13df25704134
3. European Commission (EC). *Dissemination and Exploitation Activities in Horizon 2020*, 2020 Available from: https://ec.europa.eu/research/participants/data/ref/h2020/other/events/2018-09-21/9_dissemination-exploitation-activities_en.pdf
4. Chavarría, C., et al., *Prevalence and Factors Associated With Fatigue in Patients With Inflammatory Bowel Disease: A Multicentre Study.* Journal of Crohn's and Colitis, 2019. **13**(8): p. 996-1002.
5. Davis, S.P., et al., *Influencing Factors of Inflammatory Bowel Disease–Fatigue: A Path Analysis Model.* Nursing research, 2021. **70**(4): p. 256.
6. Morgan, C., et al., *Individuals living with lupus: findings from the LUPUS UK Members Survey 2014.* Lupus, 2018. **27**(4): p. 681-687.
7. Hewlett, S., et al., *Fatigue in rheumatoid arthritis: time for a conceptual model.* Rheumatology, 2011. **50**(6): p. 1004-1006.
8. Chong, R., et al., *The dimensionality of fatigue in Parkinson's disease.* Journal of Translational Medicine, 2018. **16**(1): p. 192.
9. Glidden, A.M., et al., *Patient-reported impact of symptoms in Huntington disease: PRISM-HD.* Neurology, 2020. **94**(19): p. e2045-e2053.
10. Cormier, R.E., *Clinical methods: The history, physical, and laboratory examinations*. 3rd ed. 1990: Boston: Butterworths.
11. Seror, R., et al., *EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome.* Annals of the rheumatic diseases, 2011. **70**(6): p. 968-972.
12. Tinsley, A., et al., *Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease.* Alimentary pharmacology & therapeutics, 2011. **34**(11-12): p. 1328-1336.
13. Mantovani, S., et al., *An overview of sleep and circadian dysfunction in Parkinson's disease.* Journal of sleep research, 2018. **27**: p. e12673.
14. Schrempf, W., et al., *Sleep Disorders in Parkinson's Disease.* Journal of Parkinson's Disease, 2014. **4**(2): p. 211-221.
15. Krupp, L.B., et al., *The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus.* Archives of Neurology, 1989. **46**(10): p. 1121-1123.
16. Castillo-Cejas, M.D., et al., *Questionnaires for measuring fatigue and its impact on health perception in inflammatory bowel disease.* Revista Española De Enfermedades Digestivas, 2013. **105(3)**: p. 144–153.
17. Rundo, J.V., and Downey, R., *Chapter 25 - Polysomnography.* Handbook of Clinical Neurology, 2019. **160**: p. 381-392.
18. Corlateanu, A., et al., *To sleep, or not to sleep – that is the question, for polysomnography.* Breathe, 2017. **13**(2): p. 137.

19. European Medicines Agency (EMA). *EMA/CHMP/16274/2009 - Guideline on medicinal products for the treatment of insomnia*, 2011 Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-medicinal-products-treatment-insomnia_en.pdf.
20. Kinnucan, J.A., Rubin, D.T., and Ali, T., *Sleep and inflammatory bowel disease: exploring the relationship between sleep disturbances and inflammation.* Gastroenterology & hepatology, 2013. **9**(11): p. 718.
21. Fass, R., et al., *Sleep disturbances in clinic patients with functional bowel disorders.* The American journal of gastroenterology, 2000. **95**(5): p. 1195-1200.
22. Goldsmith, G., and Levin, J.S., *Effect of sleep quality on symptoms of irritable bowel syndrome.* Digestive diseases and sciences, 1993. **38**(10): p. 1809-1814.
23. Ali, T., and Orr, W.C., *Sleep disturbances and inflammatory bowel disease.* Inflammatory bowel diseases, 2014. **20**(11): p. 1986-1995.
24. Banovic, I., et al., *Personality and fatigue perception in a sample of IBD outpatients in remission: A preliminary study.* Journal of Crohn's and Colitis, 2012. **6**(5): p. 571-577.
25. Landers, M., Dorsey, R., and Saria, S., *Digital Endpoints: Definition, Benefits, and Current Barriers in Accelerating Development and Adoption.* Digital Biomarkers, 2021. **5**(3): p. 216-223.
26. Boehme, P., et al., *How soon will digital endpoints become a cornerstone for future drug development?* Drug Discovery Today, 2019. **24**(1): p. 16-19.
27. CTTI-DigitalHealthTrials. *Developing Novel Endpoints Generated by Digital Health Technology for Use in Clinical Trials*, n.d Available from: https://ctti-clinicaltrials.org/wp-content/uploads/2022/03/CTTI-Digital-Health-Trials-Novel-Endpoint-Acceptance-Recommendations.pdf.
28. IDEA-FAST. *WP4 – Device specific Data Analytics and Performance Assessment. D4.1: Definition of assessment protocol for device-specific digital endpoints*, 2020 Available from: https://idea-fast.eu/wp-content/uploads/2022/01/IDEA-FAST_D4.1_Definition-of-Assessment-Protocol_v1.0.pdf.
29. Inan, O., et al., *Digitizing clinical trials.* NPJ digital medicine, 2020. **3**(1): p. 1-7.
30. Coravos, A., Khozin, S., and Mandl, K.D., *Developing and adopting safe and effective digital biomarkers to improve patient outcomes.* NPJ digital medicine, 2019. **2**(1): p. 14.
31. Anderson, D., Fox, J., and Elsner, N. *Transforming the future of clinical development*. 2018. Deloitte. Available from: https://www2.deloitte.com/us/en/insights/industry/life-sciences/digital-research-and-development-clinical-strategy.html.
32. Advisory Board. *Our take: Janssen just launched its first entirely digital clinical trial*, 2019 Available from: https://www.advisory.com/daily-briefing/2019/11/21/digital-trial.
33. Kruizinga, M.D., et al., *Development of Novel, Value-Based, Digital Endpoints for Clinical Trials: A Structured Approach Toward Fit-for-Purpose Validation.* Pharmacological Reviews, 2020. **72**(4): p. 899.
34. Izmailova, E.S., Wagner, J.A., and Perakslis, E.D., *Wearable devices in clinical trials: hype and hypothesis.* Clinical Pharmacology & Therapeutics, 2018. **104**(1): p. 42-52.
35. Van Den Wijngaart, L.S., et al., *A virtual asthma clinic for children: fewer routine outpatient visits, same asthma control.* European Respiratory Journal, 2017. **50**(4).
36. Kruizinga, M., et al., *Towards remote monitoring in pediatric care and clinical trials—Tolerability, repeatability and reference values of candidate digital endpoints derived from physical activity, heart rate and sleep in healthy children.* PloS one, 2021. **16**(1): p. e0244877.
37. Myerson, R.B., *Perspectives on mechanism design in economic theory.* American Economic Review, 2008. **98**(3): p. 586-603.

38. Porter, M.E., and Kramer, M.R., *Advantage.* Creating and Sustaining Superior Performance, Simons, 1985: p. 56-68.
39. Jakub, S., Viera, B., and Eva, K., *Economic Value Added as a measurement tool of financial performance.* Procedia Economics and Finance, 2015. **26**: p. 484-489.
40. von der Schulenburg, J.-M.G., et al., *Deutsche Empfehlungen zur gesundheitsökonomischen Evaluation-dritte und aktualisierte Fassung des Hannoveraner Konsens.* Gesundheitsökonomie & Qualitätsmanagement, 2007. **12**(05): p. 285-290.
41. Mishan, E.J., and Quah, E., *Cost-benefit analysis*. 2020: Routledge.
42. Rogers, P.J., Stevens, K., and Boymal, J., *Qualitative cost–benefit evaluation of complex, emergent programs.* Evaluation and program planning, 2009. **32**(1): p. 83-90.
43. Partinen, M., et al., *Sleep and daytime problems during the COVID-19 pandemic and effects of coronavirus infection, confinement and financial suffering: a multinational survey using a harmonised questionnaire.* BMJ Open, 2021. **11**(12): p. e050672.
44. Deloitte. *Seeds of change. Measuring the return from pharmaceutical innovation 2020*. 2021. Deloitte Centere for Health Solutions. Available from: https://www2.deloitte.com/content/dam/Deloitte/us/Documents/deloitte-uk-measuring-the-return-from-pharmaceutical-innovation-2021.pdf.
45. Orloff, J.J., and Stanski, D., *Innovative approaches to clinical development and trial design.* Ann Ist Super Sanita, 2011. **47**(1): p. 8-13.
46. OECD. *Pharmaceutical spending (indicator)*, 2022 Available from: https://data.oecd.org/healthres/pharmaceutical-spending.htm.
47. Martin, L., et al., *How much do clinical trials cost.* Nat Rev Drug Discov, 2017. **16**(6): p. 381-382.
48. Goërtz, Y.M.J., et al., *Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study.* Scientific Reports, 2021. **11**(1): p. 20977.
49. Foley, D., et al., *Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey.* Journal of Psychosomatic Research, 2004. **56**(5): p. 497-502.
50. Markwald, R.R., et al., *Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain.* Proceedings of the National Academy of Sciences, 2013. **110**(14): p. 5695-5700.
51. Hafner, M., et al., *Why sleep matters the economic costs of insufficient sleep: A cross-country comparative analysis.* Rand health quarterly, 2016. **6**(4).
52. Havlikova, E., et al., *Impact of fatigue on quality of life in patients with Parkinson's disease.* European Journal of Neurology, 2008. **15**(5): p. 475-480.
53. Habibi, F., et al., *Quality of life in inflammatory bowel disease patients: A cross-sectional study.* Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences, 2017. **22**.
54. Deutsche Stiftung Schlaf. *Forsa-Umfrage Mai 2018 – Schlafstörungen*, 2018 Available from: https://deutschland-schlaeft-gesund.de/wp-content/uploads/2018/06/180620_DSG_Pressekonferenz_Handout.pdf.
55. DAK-Gesundheit. *Müdes Deutschland: Schlafstörungen steigen deutlich an. Hamburg: Pressestelle DAK-Gesundheit*, 2017 Available from: https://www.dak.de/dak/download/pressemeldung-gesundheitsreport-2017-2108942.pdf
56. Maisel, P., Baum, E., and Donner-Banzhoff, N., *Fatigue as the chief complaint: Epidemiology, Causes, Diagnosis and Treatment. Ärtzeblatt.* Deutsches Ärzteblatt International, 2021. **118**(33-34): p. 566.
57. Grobe, T.G., Steinmann, S., and Gerr, J. *BARMER Gesundheitsreport 2019: Schlafstörungen*. 2019. Barmer. Available from:

https://www.barmer.de/blob/200600/be5371374ee8e7463bb077cb6567b843/data/dl-gesundheitsreport2019.pdf

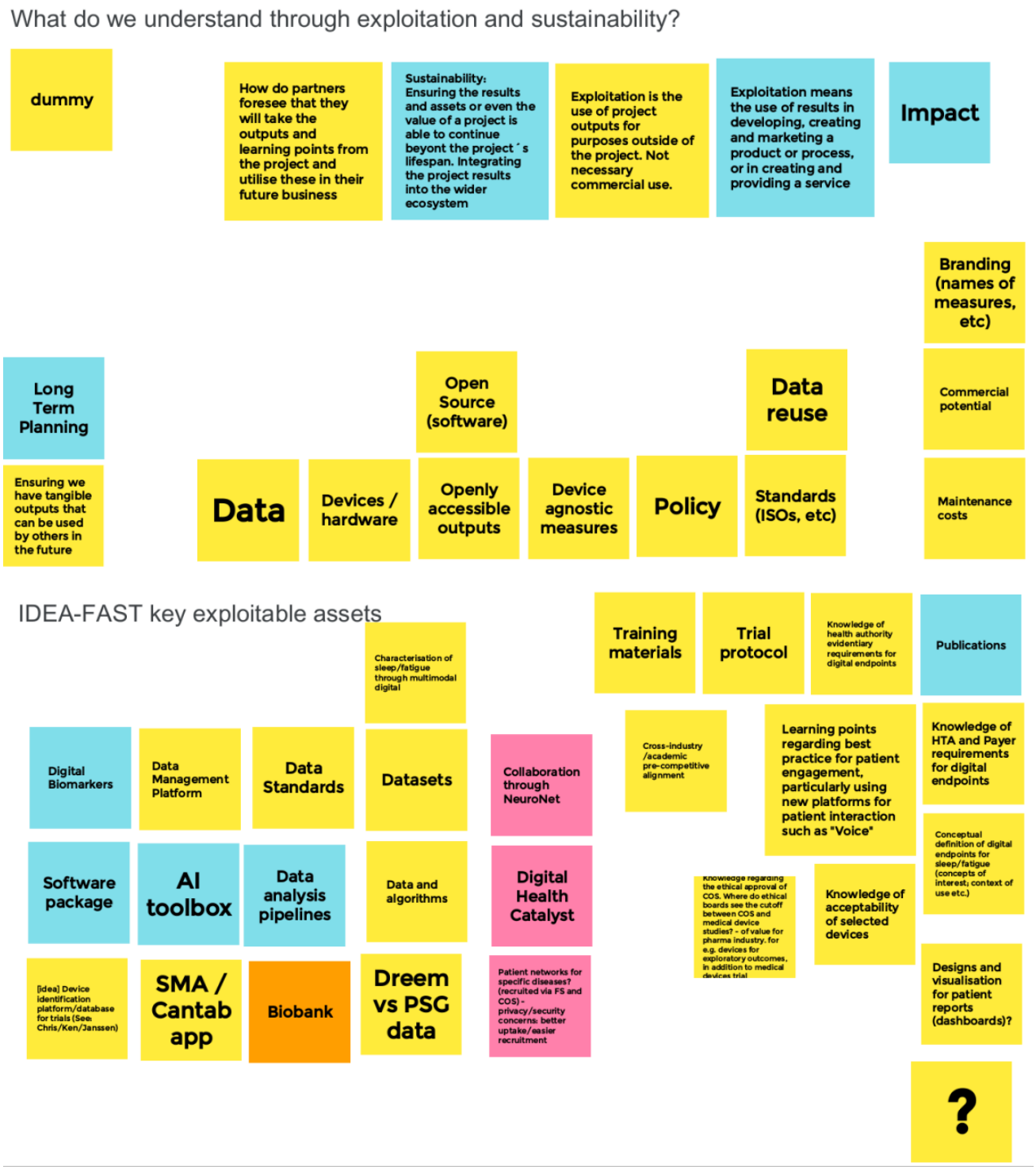
58. van de Straat, V., and Bracke, P., *How well does Europe sleep? A cross-national study of sleep problems in European older adults.* International Journal of Public Health, 2015. **60**(6): p. 643-650.
59. Federal Office of Statistics. *Krankheitskosten: Deutschland, Jahre, Krankheitsdiagnosen (ICD-10)*, 2015 Available from: https://www-genesis.destatis.de/genesis//online?operation=table&code=23631-0001&bypass=true&levelindex=0&levelid=1611067803374#abreadcrumb.
60. Gesundheitsberichterstattung des Bundes. *Diagnosedaten der Krankenhäuser nach Behandlungsort (ICD10-3-Steller, ab 2000)*, 2018 Available from: https://www.gbe-bund.de/gbe/pkg_olap_tables.prc_set_hierlevel?p_uid=gastg&p_aid=776506&p_sprache=D&p_help=2&p_indnr=544&p_ansnr=54108266&p_version=2&p_dim=D.946&p_dw=14494&p_direction=drill.
61. Federal Ministry of Health. *Zuzahlungsregelungen der gesetzlichen Krankenversicherung*, 2017 Available from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/A/Arzneimittelversorgung/Zuzahlungsregelungen_der_GKV.pdf.
62. Federal Office of Statistics. *Fallpauschalbezogene Krankenhauststatistik (DRG-Statistik): Operationen und Prozeduren der vollstationären Patientinnen und Patienten in Krankenhäusern (4-Steller)*, 2020 Available from: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankenhaeuser/Publikationen/Downloads-Krankenhaeuser/operationen-prozeduren-5231401197014.pdf?__blob=publicationFile.
63. SeegartenKlinik. *Schlaflabor Kosten – womit muss man rechnen?*, 2020 Available from: https://schlafapnoe.de/schlaflabor-kosten-womit-muss-man-rechnen/.
64. Kassenärztliche Bundesvereinigung. *Kardiorespiratorische Polysomnographie*, 2022 Available from: https://www.kbv.de/tools/ebm/html/30901_2903842213874606140416.html.
65. Kassenärztliche Bundesvereinigung. *Kardiorespiratorische Polygraphie*, 2022 Available from: https://www.kbv.de/tools/ebm/html/30900_2904532700272440246l4.html.
66. Reimbursement.info. *E63 – Schlafapnoesyndrom oder Polysomnographie oder Polygraphie bis 2 Belegungstage*, 2021 Available from: https://app.reimbursement.info/drgs/E63?year=2021.
67. INTERSOM-Köln. *Infopool Schlaf*, 2021 Available from: https://intersom.de/en/.
68. Wohlers, K., and Hombrecher, M. *Schlaf gut Deutschland, TK-Schlafstudie 2017*. 2017. Techniker Krankenkasse. Available from: https://www.tk.de/presse/themen/praevention/gesundheitsstudien/tk-schlafstudie-2017-2036638.
69. MedBill. *EBM Ziffer - 03005*, 2022 Available from: https://app.medbill.de/ebm-ziffern/236,%20retrieved%20March%202022.
70. MedBill. *EBM Ziffer - 03004*, 2022 Available from: https://app.medbill.de/ebm-ziffern/235.
71. MedBill. *EBM Ziffer - 03003*, 2022 Available from: https://app.medbill.de/ebm-ziffern/234.
72. KBV. *Zusatzpauschale zu der Gebührenordnungsposition 03040*, 2022 Available from: https://www.kbv.de/tools/ebm/html/03060_2901663936176340913632.html.
73. KBV. *Zusatzpauschale zur GOP 03060*, 2022 Available from: https://www.kbv.de/tools/ebm/html/03061_2902679439824648333088.html.
74. KBV. *Zusatzpauschale zu den Gebührenordnungspositionen 03000 und 03030 für die Wahrnehmung des hausärztlichen Versorgungsauftrags gemäß § 73 Abs. 1 SGB V*, 2022 Available from: https://www.kbv.de/tools/ebm/html/03040_2901998982473615086560.html.

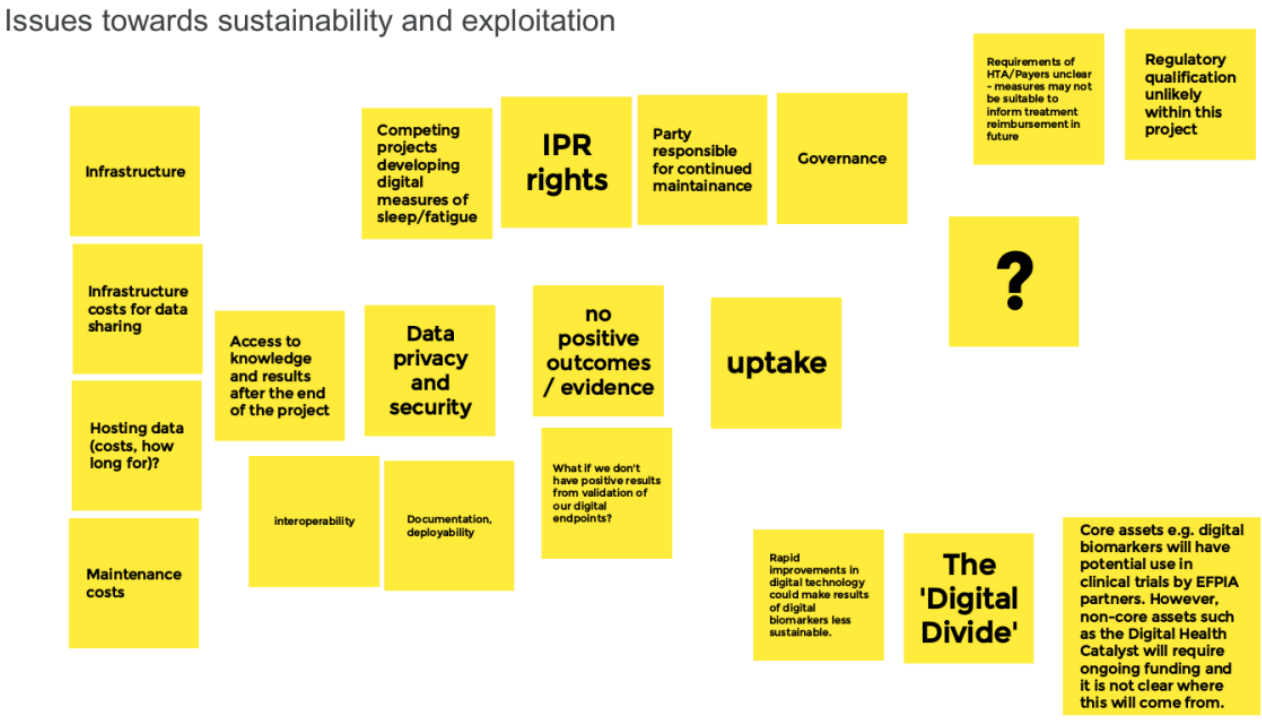
75. GKV-Spitzenverband. *Fokus: Ambulante Psychotherapie*, 2021 Available from: https://www.gkv-spitzenverband.de/gkv_spitzenverband/presse/fokus/psychotherapie.jsp.
76. Derprivatpatient.de. *Psychotherapie: Welche Behandlungen übernimmt die PKV?*, 2019 Available from: https://www.derprivatpatient.de/infothek/nachgefragt/psychotherapie-welche-behandlungen-uebernimmt-die-pkv.
77. Psychomeda. *Was kostet Psychotherapie – und wer zahlt?*, 2020 Available from: https://www.psychomeda.de/psychotherapie/was-kostet-psychotherapie.html.
78. Marschall, J., et al., *Gesundheitsreport 2017, Analyse der Schlafunfähigkeitsdaten. Update: Schlafstörungen. Beiträge zur Gesundheitsökonomie und Versorgungsforschung (Band 16).* 2017: p. 70.
79. Federal Ministry of Health. *The German healthcare system*, 2020 Available from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Broschueren/200629_BMG_Das_deutsche_Gesundheitssystem_EN.pdf.
80. Riemann, D., et al., *S3-Leitlinie Nicht erholsamer Schlaf/Schlafstörungen.* 2017.
81. Weiß, V., and Hauswaldt, J., *Off-record prescription of hypnotics: analysis from family physicians' electronic health records.* 2015: p. 408-412.
82. Statista. *Anzahl der Erwerbstätigen in Deutschland nach dem Inlandskonzept von 1991 bis 2019*, 2021 Available from: https://de.statista.com/statistik/daten/studie/214465/umfrage/erwerbstaetige-in-deutschland-nach-inlandskonzept/.
83. Statista. *Krankheitsbedingte Fehltage im Jahr je Arbeitnehmer in Deutschland von 1991-2019*, 2021 Available from: https://de.statista.com/statistik/daten/studie/13441/umfrage/entwicklung-der-jaehrlichen-anzahl-krankheitsbedingter-fehltage-je-arbeitnehmer/.
84. Busse, R., and Blümel, M., *Germany: health system review*. 2014. **16**(2): p. 1-296.
85. White, B., et al., *Risk of cancer following primary care presentation with fatigue: a population-based cohort study of a quarter of a million patients.* British Journal of Cancer, 2022.
86. Dyas, J.V., et al., *Patients' and clinicians' experiences of consultations in primary care for sleep problems and insomnia: a focus group study.* British Journal of General Practice, 2010. **60**(574): p. e180.
87. Hayward, R., Jordan, K.P., and Croft, P., *Healthcare use in adults with insomnia: a longitudinal study.* British Journal of General Practice, 2010. **60**(574): p. 334.
88. Aviva. *Health Check UK Report*, 2016 Available from: https://static.aviva.io/content/dam/aviva-corporate/documents/newsroom/pdfs/newsreleases/2003/Aviva_Health_Check_Report_SECURED_13.10.16.pdf.
89. Carlos, R.-P.J., Martina, G., and Jon, S., *Obstructive Sleep Apnoea Health Economics Report.* 2014.
90. Fineberg, N.A., et al., *The size, burden and cost of disorders of the brain in the UK.* Journal of Psychopharmacology, 2013. **27**(9): p. 761-770.
91. 20/20Health.org and The Optimum Health Clinic Foundation. *Counting The Cost: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis*, 2017 Available from: https://www.theoptimumhealthclinic.com/wp-content/uploads/2017/09/Counting-the-Cost.pdf.
92. NHS England and NHS Improvement. *NHS Diagnostic Waiting Times and Activity Data*, 2021 Available from: https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2021/02/DWTA-Report-December-2020.pdf.
93. Steier, J., et al., *Predicted relative prevalence estimates for obstructive sleep apnoea and the associated healthcare provision across the UK.* Thorax, 2014. **69**(4): p. 390.

94. Nuffield Health. *Sleep study and investigations at Brentwood Hospital*, n.d Available from: https://www.nuffieldhealth.com/hospitals/brentwood/treatments/sleep-study-and-investigations.
95. NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*, 2019 Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20.
96. NHS Digital. *NHS Hospital Admitted Patient Activity, 2020-2021, Diagnosis*, 2021 Available from: https://files.digital.nhs.uk/D9/DD187B/hosp-epis-stat-admi-diag-2020-21-tab.xlsx.
97. BBC. *Bed-blocking patient evicted after two years 'did not want to stay'*. 2017: Norfolk. Available from: https://www.bbc.com/news/uk-england-norfolk-38731937.
98. Manoukian, S., et al., *Bed-days and costs associated with the inpatient burden of healthcare-associated infection in the UK.* Journal of Hospital Infection, 2021. **114**: p. 43-50.
99. NHS. *About NHS hospital services*, 2019 Available from: https://www.nhs.uk/nhs-services/hospitals/about-nhs-hospital-services/.
100. Basu, N., et al., *Fatigue is associated with excess mortality in the general population: results from the EPIC-Norfolk study.* BMC Medicine, 2016. **14**(1): p. 122.
101. Elmore, N., et al., *Investigating the relationship between consultation length and patient experience: a cross-sectional study in primary care.* The British journal of general practice : the journal of the Royal College of General Practitioners, 2016. **66**(653): p. e896-e903.
102. Personal Social Services Research Unit of the University of Kent. *II. COMMUNITY-BASED HEALTH CARE STAFF*, 2020 Available from: https://www.pssru.ac.uk/pub/uc/uc2020/2-communityhcstaff.pdf.
103. NHS. *Insomia*, 2021 Available from: https://www.nhs.uk/conditions/insomnia/.
104. National Institute for Health and Care Excellence (NICE). *Healthapp: Sleepio for adults with poor sleep*, n.d Available from: https://www.nice.org.uk/advice/mib129/chapter/Costs-and-resource-use.
105. NHS. *Overview - Cognitive behavioural therapy (CBT)*, 2019 Available from: https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/talking-therapies-and-counselling/cognitive-behavioural-therapy-cbt/overview/.
106. NHS. *NHS prescription charges*, 2021 Available from: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/nhs-prescription-charges/.
107. NHS. *Who can get free prescriptions*, 2021 Available from: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/.
108. National Institute for Health and Care Excellence (NICE). *Hypnotics*, 2021 Available from: https://www.nice.org.uk/advice/ktt6/resources/hypnotics-pdf-1632173521093.
109. The Innovative Medicines Initiative (IMI). *The Innovative Medicines Initiative (IMI) Strategic Research Agenda. Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society*, 2008 Available from: http://vhir.org/DDGRecerca/DOCENCIAACTIVITATS/2008/2008_0042/2008_0042_005.pdf.
110. The Innovative Medicines Initiative (IMI). *Scaling Innovations emerging from public-private partnerships – A Field Manual*, 2021 Available from: https://www.imi.europa.eu/sites/default/files/events/2021/20211026_Masterclass/Scaling%20PPP%20Innovation%20Field%20Manual.pdf.
111. IDEA-FAST. *WP5 – Data management. D5.2 Data management platform specification*, 2020 Available from: https://idea-fast.eu/wp-content/uploads/2022/01/IDEA-FAST_D5.2_DMP-Specification_v1.0.pdf.

112. IDEA-FAST. *WP5 – Data Management, D5.1 Data Management Plan*, 2020 Available from: https://idea-fast.eu/wp-content/uploads/2021/01/IDEA-FAST_D5.1-IDEA-FAST_DMP_v10.pdf.
113. Neuronet. *Neuronet Knowledge base*, n.d Available from: https://kb.imi-neuronet.org/.
114. VOICE. *Harnessing Human Experience*, 2022 Available from: https://www.voice-global.org/.
115. Payne, A., Frow, P., and Eggert, A., *The customer value proposition: evolution, development, and application in marketing.* Journal of the Academy of Marketing Science, 2017. **45**(4): p. 467-489.
116. IDEA-FAST. *WP4 – Device specific Data Analytics and Performance Assessment, D4.4. Requirements specification data analytics software package*, 2021 Available from: https://idea-fast.eu/wp-content/uploads/2022/04/IDEA-FAST_D4.4_RequirementsSpecificationDataAnalyticsSW_V1.0.pdf.
117. IDEA-FAST. *WP8 – Data Protection, Ethics, and Legal Challenges, D8.1 The model informed consent for the FS*, 2020 Available from: https://idea-fast.eu/wp-content/uploads/2021/01/IDEA-FAST_D8.1-Model-Informed-Consent-for-the-FS-V1.pdf.
118. Fourie, F., and Burger, P., *An economic analysis and assessment of public-private partnerships (PPPs).* South African Journal of Economics, 2000. **68**(4): p. 305-316.
119. Underdal, A., *Integrated marine policy: what? why? how?* Marine Policy, 1980. **4**(3): p. 159-169.
120. Greenhalgh, T., et al., *Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies.* Journal of medical Internet research, 2017. **19**(11): p. e8775.
121. Greenhalgh, T., and Shaw, S., *Understanding heart failure; explaining telehealth–a hermeneutic systematic review.* BMC cardiovascular disorders, 2017. **17**(1): p. 1-16.

Appendix A – Exploitation and Impact Sub-committee Jamboard presentation




Issues towards sustainability and exploitation
Infrastructure
Competing projects developing digital measures of sleep/fatigue
IPR rights
Party responsible for continued maintainance
Governance
Requirements of HTA/Payers unclear - measures may not be suitable to inform treatment reimbursement in future
Regulatory qualification unlikely within this project
?
Infrastructure costs for data sharing
Access to knowledge and results after the end of the project
Data privacy and security
no positive outcomes / evidence
uptake
Hosting data (costs, how long for)?
What if we don't have positive results from validation of our digital endpoints?
interoperability
Documentation, deployability
Maintenance costs
Rapid improvements in digital technology could make results of digital biomarkers less sustainable.
The 'Digital Divide'
Core assets e.g. digital biomarkers will have potential use in clinical trials by EFPIA partners. However, non-core assets such as the Digital Health Catalyst will require ongoing funding and it is not clear where this will come from.

Appendix B – Key exploitable assets Questionnaire

1. Title of output/asset

   Please enter a meaningful title of your output / asset (between 20 and 200 characters, spaces included).e.g. IDEA-FAST participant secure portal; IDEA-FAST data management platform;

2. The output/asset is a result of which WP(s)?

3. Describe the output/asset

   Please provide a short description for the outcome/asset that you have produced or expect to produce as part of your work, including any innovative aspects.

4. Who will benefit from your work/your asset? Who accesses your work and how will it be accessed? Whenever possible, please specify the type of user in some more detail, and briefly elaborate on the expected use case for the group of users described.

5. How do you see your output/asset being utilised?

6. Does an intellectual property rights (IPR) co-ownership exist with external partners (e.g., via an OS licence, a commercial licence, for a price/yearly fee, etc.) or IDEA-FAST project partners, or a third party?

7. Who is the IPR owner of the output/asset? Please also list any foreseeable conflicts or issues regarding IPR in your assets. Have you already considered any form of licensing?

8. What will be the technological readiness level by the end of the project?

9. Additional opportunities

   Please outline additional opportunities you see to capitalise on intended IDEA-FAST results for you or IDEA-FAST as a whole.

Appendix C – Key exploitable assets overview from partner contributions

Table Legend:

Title	Please enter a meaningful title of your output / asset (between 20 and 200 characters, spaces included).
WP	The output/asset is a result of which WP?
Description	Please provide a short description for the outcome/asset that you expect to produce as part of your work.
Who will benefit?	Who will benefit from your work/your asset? Who accesses your work and how will it be accessed? Whenever possible, please specify the type of user in some more detail, and briefly elaborate on the expected use case for the group of users described. Example categories: Research, Healthcare (patients, GPs, hospital, insurances, ...), Industry (IT, pharma, devices, ...)
How?	How do you see your output/asset being utilised? Examples: improved patient self-management, cost-reduction, increased health literacy, new business opportunities, policy advice, etc. ...
IPR/IPR-ownership	Does an intellectual property rights (IPR) co-ownership exist with external partners (e.g. via an OS licence, a commercial licence, for a price/yearly fee, etc.) or Gravitate Health project partners, or a third party? If yes, who is the IPR owner of the output/asset? Please also list any foreseeable conflicts or issues regarding IPR in your assets. Have you already considered any form of licensing?

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
Digital Biomarkers designed from COS	WP2 WP4 WP7	Knowledge with supporting software: one key aim of the COS is to result in the identification of candidate digital biomarkers and endpoints built from digital features which can be used to predict / replace sleep or fatigue references. Supporting biomarkers computation scripts in Python	If successful, all the stakeholders will benefit. clinical research, pharma industry, device manufacturers, as well as hospitals (such biomarkers will eventually be used of modify to assess treatments and/or improve care), patients (digital endpoints better centered on their quality of life)	Improvement treatments, new endpoints for pharma industry for drug development, candidate for regulatory acceptance or qualification, improved patient self-management, improvement care pathways.	There is no IP on biomarkers per se. Biomarkers are only patented when coupled with a treatment or a diagnosis.
Data Analytics Package	WP4 WP5 WP7	This is a data product. This is essentially the COS study data packaged in a standard format that could but submitted to regulators in the future. It is currently unclear whether such a data analytics package will be required for submission to EMA as part of regulatory interactions.	Anyone who wants to use the data from the COS in the context of a regulatory interaction (likely primarily Pharma industry)	Regulatory interactions	Not known

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
Development of an AI Toolbox for robust multi-variate time-series analysis	WP7	An AI Toolbox for multi-variate time-series analysis will be developed, including AI methods for: - handling of poor-quality signals - earning personal activity patterns - Robust ML approaches for weakly annotated data - Multimodal data aggregation and visualisation of heterogeneous data sources - handling multi-variate, weakly annotated time-series analysis of personal data - time-series data related with not completely reliable ground truth (PROs) The Ai toolbox plays a key role in mapping the information collected from the digital devices to the Patient Reported Outcomes, Knowledge: scientific articles describing the proposed solutions.	Research communities, pharma and MD industry, device manufacturers, patients.	ML/AI approaches are useful tools for transforming raw signals into actionable information and combinatory algorithms will be developed to accommodate different sensing modalities. The purpose of the proposed algorithms is to improve the identification of some elements of the patient's state of health (quality of sleep, fatigue, etc.), starting from the data acquired by the devices. Improving these algorithms can result in more accurate monitoring of the evolution of the patient's state of health.	
Data analysis pipeline, data analysis software package	WP4				

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
Data management platform		The IDEA-FAST Data Management Platform (DMP) is designed and developed by WP5 to address the needs of data management for the IDEA-FAST project. All data generated in the IDEA-FAST project is expected to be integrated and stored on the DMP using a secure and robust process that is fully compliant with European data privacy and security legislation and standards, in particular the General Data Protection Regulation (GDPR).	Research communities, Pharma and MD Industry	DMP is developed under MIT license with very limited restriction on reuse. Any research projects involving healthcare data management and curation would benefit from adopting DMP.	Not known
Data standards		The data standards are designed for the clinical studies of the IDEA-FAST project with respect to sleep/fatigue/activities of daily living (ADL) and the ontology for sensor measurements. The data standards defined are based on the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC).	Research communities, Pharma and MD Industry	The data standards are developed for improving data quality and efficiency of data analysis. The IDEA-FAST data standards are freely accessible and can be used to standardise sleep/fatigue/ADL related clinical and device data collected by other studies.	There is no IP on data standards.
Digital biobank: Various datasets, Clinical datasets		A digital biobank on multi-modal data on 6 patient cohorts from 17 centres across 10 countries within Europe, representing geographic, ethnic and healthcare diversity.	Research communities, Pharma and MD Industry	The digital biobank will be invaluable for disease stratification, which in turn will lead to new approaches to disease assessment with high exploitation potential for academia and industry.	
Infrastructure: Biobank/Bioresources		Biobank consisting from blood, urine and stool samples from 6 patient cohorts, 17 centres across 10 countries within Europe, representing geographic, ethnic and healthcare diversity (Both from FS and COS)	Research communities, Pharma and MD Industry		

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
Feasibility Study results		The result of the feasibility study has demonstrated to which extent digital devices and PROs can be assessed in parallel without adding too much burden on patients (and also where the limits are). It has shown which type of devices and respective complexity are suitable for which patient group depending on their disease. In addition, this study provides a good estimate of the data quality and completeness that can be expected in such a setting which will facilitate sample size calculations for future studies. Lessons learnt from this study (e.g., level and extent of patient support material and training of staff) will help to create targeted supportive material for patients and study staff which is the basis for good recruitment and quality of data capturing			
Feasibility study analysis	WP 7	Knowledge with supporting software. The FS analysis includes: • Initial analysis plan • FS data preparation • Assessment of variability from FS observations • Analysis to identify predictors of sleep and fatigue references Supporting Python scripts	The FS analysis is useful for clinical research and for data scientists. It is valuable to design clinical studies in the spirit of the COS which can take advantage of the FS preliminary findings. The methods to identify reference predictors as well as their Python implementation are of interest.	Use results and methods for the design of clinical trials and analysis plans. Use of code could be provided as an example to get started with analysing the FS data for future researchers.	Available for the consortium partners. The Python scripts are on the Idea-Fast GitHub.
Scientific publications resulting from FS analysis	WP2 WP4 WP7	Scientific articles, therefore, knowledge, resulting from collaborations between WP7 (data scientists & statisticians), WP4 (data scientists & signal processing), and WP2 (clinical partners) to identify the most useful or intriguing results from the analysis of FS observations.	Scientific Research Community.	Clinical trial analysis and design, knowledge creation, support for lowering barriers between clinicians and data scientists.	N/A The plan is to have these published in academic research journals.

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
Statistical analysis plan template and methodologies	WP7	Knowledge and potentially templates of a statistical analysis plan (SAP) based on the FS and COS.	Scientific Research Community. (Anyone who wants to create an analysis plan for future similar studies focused on biomarker identification and/or evaluation.)	A template could be created and provided as a resource to companies who are planning similar studies in the future.	
Knowledge of acceptability of selected devices, knowledge on design and use of visualisations for participants	WP3				
List of extant academic and literature datasets	WP7	Knowledge. Compilation of relevant datasets identified in relation with the project which can be used to either assess the variability of corresponding digital observations or experiment the design of digital features. Observations may come from healthy patients or from patients suffering from pathologies targeted by IDEA-FAST (or closely related diseases). Deliverable 7.6 will list the datasets (including EFPIA contributed datasets) and will be confidential to consortium (though some datasets may be publicly available)	Statisticians and data scientists can benefit from these datasets by testing preliminary hypotheses and assessing the level of variability, noise, data quality challenges before designing a study.	First it can be used as a review of interesting datasets that were identified, in which case it should be maintained up to date. Second when authorized some of the data itself has been compiled for Idea-Fast and does not require for every new user to request it.	Some data is available publicly or open unconditional request, some may require a research justification

Asset Title	*WP*	*Description*	*Who will benefit?*	*How it will be used?*	*IPR/IPR-ownership*
COS Study	The COS study will hopefully identify digital outcomes that may serve as clinical endpoints for EMA in a sense that they can be used during drug development as validated endpoints to assess fatigue. The qualitative advice that has been received by EMA will be built into the COS design as far as feasible and should help pave this way towards regulatory acceptability of one or several digital endpoints. Linking those results with to outcomes of the polysomnography study may further strengthen this approach. If successful IDEA FAST FS and COS can act as a blueprint for future studies assessing new digital devices as well as allowing the incorporation of such important patient centric outcomes as fatigue to be used during drug development in a large group of different diseases. As fatigue is a key problem for many patients across various diseases it is essential to have validated clinical endpoints accepted by EMA. An immediate and hopefully lasting effect of this great collaboration across academic and pharma is the increased public awareness of the burden of fatigue on QoL across many different diseases. It will hopefully spark inclusion of fatigue related endpoints in the development of new therapies to bring better medicines to patients.				
COS results publications, FS and COS Training materials and trial protocols	WP2 WP4 WP7	Scientific articles, therefore knowledge, resulting from collaborations between WP7 (data scientists & statisticians), WP4 (data scientists & signal processing), and WP2 (clinical partners) to identify the key results from the analysis of COS observations: identification of biomarkers, performance, statistical variability.	Research Communities	Clinical trial analysis and design, knowledge creation, support for lowering barriers between clinicians and data scientists, regulatory material.	N/A The plan is to have these published in academic research journals.
Knowledge regarding recruitment of patients for COS	WP6	Possible advice paper on pre-screening strategy, knowledge on inclusion and exclusion criteria to efficiently target the patients for screening, as part of the recruitment strategy	Everyone involved in clinical trials and dealing with large-scale recruitment	Improvement of recruitment and pre-screening strategy	
Knowledge regarding the ethical approval of the COS	WP6 WP8	Where do ethical boards see the cutoff between clinical observation studies and medical devices studies?	Research communities, Pharma and MD industry	Of value for research communities, pharma and MD industry for exploratory outcomes, in addition to medical devices trial	
Knowledge of Regulator, HTA and Payer requirements for digital endpoints	WP9	Official guidance is not yet provided by EMA, HTA bodies or Payers. We are developing an understanding of their requirements and gaps in current guidance through regulatory interactions, workshops and interviews	Research communities, Pharma, Regulatory Agencies, HTA bodies, Payers	This knowledge will inform how future researchers should develop and validate digital endpoints and will shape future guidance	N/A

Asset Title	*Description*	*Who?*	*How?*
Collaboration/Outreach through Neuronet	Neuronet is an IMI-funded initiative aiming to support and better integrate projects in the IMI. Neurodegenerative Disorders (ND). One of its objectives is to create an overall platform for efficient collaboration, communication and operational synergies among present and future IMI neurodegenerative diseases projects.		
Digital Health Catalyst – a collaboration between IDEA-FAST and Mobilise-FD	IDEA-FAST and Mobilise-D, which are both funded under the IMI JU2 initiative, are collaborating to establish the Digital Health Catalyst (DHC). In the first instance the DHC will be a platform that will develop and support the early career researchers (ECR's) that both academia and industry need to develop health related digital technology in the future. In addition to this the academy is seen as an excellent vehicle for sustainability and as such the scope of its function is likely to expand into areas such as technology development, setting research agendas and promoting translation into clinical practice.	The Digital Health Catalyst recognises that the work of the consortium provides a platform for ECR's (Fellows & PhD students) to grow professionally, expand their vision, enhance multi-disciplinary understanding and in turn enhance the impact on their future careers. By doing so we hope to help build the next generation of thought leaders in Mobility, Fatigue and Sleep research. Once established the Digital Health Catalyst will also reach out to other relevant IMI project for potential inclusion	ECR's contribute significantly to knowledge generation and the overall success of research projects. The Digital Health Catalyst will develop and deliver a programme of activities to ensure that our ECR's have wide exposure to the rich scientific environment in the consortium within and across the partners, but also to provide training, help to publish their work, help to design new research projects, access to project data, opportunity to build their networks, and foster thinking outside the box. By expanding the horizons of our Fellows and PhD students, we hope to contribute to faster and better research in the next decade.
Patient networks for specific diseases	Reaching out to/facilitating access to patient networks for specific diseases for easier recruitment in the future.		
IDEA-FAST clinical network	The IDEA-FAST clinical network, with capacity and expertise to perform future studies involving remote visits and use of digital technology.		
Patient engagement through the VOICE platform	Learning points regarding best practice for patient engagement.		