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PRECISE4Q

PREDICTIVE MODELLING IN STROKE

DELIVERABLE

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D4.1 – White paper on stroke risk, health and resilience factors

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Abstract (for dissemination)	This document presents the so far defined updated use cases for modelling, our definitions for risk, health and resilience factors and a comprehensive overview of potentially relevant features for all phase of the stroke patient journey. This will - together with D4.2. - facilitate the modelling endeavours within P4Q by providing a common ground for discussion, model building and study planning.
Keywords	risk factors, health factors, resilience factors, prevention, acute stroke treatment, rehabilitation, reintegration

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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Executive Summary

PRECISE4Q set out to minimise the burden of stroke for the individual and for society. It will create multi-dimensional data-driven predictive machine learning models enabling – for the first time – personalised stroke treatment, addressing patient needs in four stages: prevention, acute treatment, rehabilitation and reintegration. A very important prerequisite for the predictive modelling outlined in P4Q for each stroke stage is the definition of the use cases. A use case defines the setting where a model will be used, thus defining the possible features and targets. In D4.1 we focus on the potential features of the models which will be developed in PRECISE4Q, whereas in D4.2 we focus on the targets.

In this deliverable, we first outline in *chapter 1* the use cases according to the 4 stroke patient journey points. For **prevention**, aligned with T4.5, we outline the primary and secondary prevention use cases, where features are very similar. However, for secondary prevention more routinely acquired data is available, most importantly neuroimaging from the time of acute stroke treatment. Also, we emphasize that - under the right circumstances of proven causality - the prediction of compliance to risk-mitigating and health-improving interventions might serve as a surrogate target instead of predicting stroke risk directly, which is problematic due to the involved long time horizons. Lastly, we highlight in the use cases the use of hybrid modelling fusion strategies, which are focused on in detail in D4.4. For **acute stroke** treatment, we outline the use cases according to the tasks T4.6 and T.4.7. While the targets differ - please see D4.2 for details - the features for these tasks, and thus the different use cases are the same. We can utilize clinical data, neuroimaging, simulated brain perfusion information for hybrid modelling and, importantly, the information about the individual treatment of the patient. For **rehabilitation** and **reintegration** the use cases focus on the prediction of risks, compliance and outcome, and psycho-social status and acceptance into the community, respectively. Here, next to risk and health factors also resilience factors play a role.

Thus, in *chapter 2* of this deliverablewe define - before listing all features - how we define risk factors, health factors and resilience factors. While the definitions is relatively straightforward for risk factors, health and resilience factors prove a bigger challenge due to lacking or conflicting use in the literature. Briefly, we define risk factors as actively present features associated with increasing the risk of stroke, health factors as actively present features which are associated with decreasing the risk of stroke, whereas resilience features are associated with good recovery after stroke.

Finally, we give an comprehensive overview of all potential features for each of the 4 stroke phases in *chapter 3*.

Taken together, this deliverable will facilitate the modelling endeavours within P4Q by providing a common ground for discussion, initial model building and study planning.

Scope and Purpose

PRECISE4Q set out to minimise the burden of stroke for the individual and for society. It will create multi-dimensional data-driven predictive machine learning models enabling – for the first time – personalised stroke treatment, addressing patient needs in four stages: prevention, acute treatment, rehabilitation and reintegration.

A very important prerequisite for the predictive modelling outlined in P4Q for each stroke stage is the definition of the use cases. A use case defines the setting where a model will be used, thus defining the possible features and targets.

In deliverable 1.3, we have outlined the state-of-the-art for the most common use cases. As stressed in that deliverable, it is a dedicated goal of P4Q to assess this state-of-the-art critically and to update and adjust the use cases during the course of the project. Such a planned adjustment will be performed as part of this current deliverable which will outline the health, risk and resilience factors, i.e. our model features, which we will explore in the modelling phase of the project. These use case adjustments reflect new scientific developments both in the clinical and modelling field as well as the interdisciplinary work carried out within the consortium, especially to develop novel, complex markers which are not in use in the current clinical setting. Here, the use cases were specifically discussed at length within the whole consortium in the plenary meeting in Barcelona in December 2018.

The scope of this process is outlined in Objective 2 of the proposal ("To identify health factors, risk factors, resilience factors and life events in stroke affecting well-being (integrated quality-of-life-concept)":

"This objective is highly cross-disciplinary and needs to be performed prior to modelling, but iteratively in parallel to Objective 1. It entails defining the inputs and outputs for the modelling phase. First, the most likely scenarios and use cases for the clinical phases of stroke will be defined. Then, we will identify, rank and weigh input factors of stroke available in our databases in terms of both risk and resilience. The activity will consist of iterations of dialogue between clinicians and modellers. (...) Defining the outputs for the models, it is crucial to understand how the model output directly links to interventions in patient treatment and how the model fits into the treatment processes within the care setting. (...) A central motive of our study is to use a quality-of-life framework as a proxy for resilience and wellbeing. Our models will predict a set of interrelated factors that reflect the variety and evolving factors contributing to an individual's quality of life. Thus, in this objective the outputs variables will be identified, weighted and integrated in a quality-of-life framework."

To facilitate understanding of our process we will outline the so far submitted deliverables within the context of this deliverable.

D1.1. Risk factors and outcome

This deliverable summarized the scientific status regarding risk factors and targets for each phase of stroke.

D1.2. Clinical challenges and needs

Here, we outlined the clinical needs for each stroke emphasizing the most common questions.

D1.3 Use Cases with inputs/outputs

This deliverable summarized the baseline use cases which have been explored in the literature so far.

D4.1 White paper on stroke risk, health and resilience factors

This deliverable will provide a) updated use cases as a basis for deliverables 4.1, 4.2 and 4.4. and b) provide an overview which risk, health and resilience factors we will explore in the modelling phase. A major point here is the point-of-view regarding potential interventions, i.e. the implementation of better clinical care through machine learning based clinical decision support

D4.2 Defining prediction targets for the models

Whereas 4.1 focuses on the features/factors which are relevant for the use cases in 4.2. we will summarize which targets we will predict in our modelling phase. Next to existing markers - as baseline - we will explore the development of new, complex Quality of life markers within P4Q.

D4.4. Patient Outcome Heterogeneous Model Fusion Strategies

A highly promising approach for the successful development of personalized clinical decision support tools is the use of combined mechanistic simulation and phenomenological machine learning tools. Here, - based on the use cases - we will explore the possible application of hybrid models for our modelling approaches.

1 Updated Use Cases

We will start by updating the use cases outlined in D1.3 based on new scientific literature and the interdisciplinary work carried out so far in the P4Q consortium. The full content of D1.3 will not be repeated here We will instead focus mostly on additions and changes. Nevertheless, relevant text parts have been copied from D1.3.

1.1 Stroke Prevention

One of the most promising approaches to reduce the effects of stroke on individual health and healthcare systems is to prevent stroke. More than 77% of stroke events are first time events. Former epidemiologic studies have identified major overarching causes of stroke such as hypertension, cigarette smoking, diabetes, dyslipidemia, atrial fibrillation and carotid stenosis. While general recommendations can be given to patients to treat these conditions, it is currently unknown how a given patient is individually affected by these risk factors. Importantly, most of the risk factors are currently undertreated in the general population. Lifestyle modification is of particular interest for stroke prevention, as the incidence of stroke has decreased by up to 42% in developed countries within the last 30 years, whereas an increase by more than 100% has been reported in developing countries [1]. This observation indicates the important role of lifestyle and diet; the prevalence of risk factors such as smoking, hyperlipidemia, or high blood pressure has decreased considerably, thereby increasing awareness among the populations of high-income countries. However, in low income countries, industrialization has led to unfavourable food and lifestyle changes.

The other important prevention scenario is secondary prevention. Minor stroke and TIA can be considered warning events[2]. Here, it is very important to prevent the second – potentially deadly or devastating – stroke event. In contrast to the primary prevention scenario the secondary prevention scenario is different, as other – often more expensive and less frequent – diagnostics are available as inputs. Generally, it is important to mention that primary and secondary prevention of stroke is strongly tied to tertiary prevention of diseases and chronic conditions that are stroke risks at the same time. For example, the optimal tertiary prevention of hypertension and diabetes mellitus is also primary prevention of the disease stroke.

1.1.1Stroke Primary prevention

As outlined in D1.3, there is a very important distinction between modifiable and unmodifiable risk factors (See also D1.1 of the PRECISE4Q project). While unmodifiable risk factors will certainly play a role in determining the stroke risk – especially in predictive models – they are not available for interventions. In contrast, modifiable risk factors are the primary target of primary stroke prevention.

We have additionally identified three groups as stakeholders: i) the patients, ii) the healthcare professionals identifying patients at risk of stroke, as well as iii) family members, which are important especially in the case of elderly patients

As outlined in D1.1, prevention strategies for stroke have so far primarily been done from an epidemiological and public health point of view[3]. Interventions are analyzed on the population level both in terms of the interventions themselves (e.g.[4]) as well as their health-economic outcome (e.g. [5]). Prevention strategies focused on the individual patient in terms of personalized medicine are lacking[6]. A big challenge for the implementation of such personalized options are the challenges of such programs: current personalized approaches have focused on individualized management programs run by doctor's offices and outpatient clinics[6]. These, however, are expensive and imply logistical challenges, as they require multiple sessions with highly qualified staff. Regional lack of centres that can provide such programs as well as limited mobility of patients are challenging for such programs. Here, risk calculation tools with disease management functions embedded into smart phone applications can be a viable alternative[6]. Such an approach is highly promising, since according to some reports 90% of the stroke risk can be explained by 10 risk factors [7], thus optimal management of a few risk factors could reduce the stroke risk significantly and increase the understanding and compliance to treatment.

Based on the above considerations we will adjust and update the use cases for the primary prevention of stroke as follows:

1.1.1.1. Primary Prevention: Use case 1

Aim:	Prevention of stroke
Target population:	General population at risk of stroke
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Reduction of risk factors by mobile application
Success measure:	Reduction of occurence of stroke
Features:	Modifiable and un-modifiable risk factors
Targets:	Prediction of stroke risk within x years, prediction of risk-factors/compliance

1.1.1.2. Primary Prevention: Use case 2

Aim:	Prevention of stroke
Target population:	General population at risk of stroke
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Increase of health factors to reduce stroke risk
Success measure:	Reduction of occurence of stroke
Features:	Modifiable and un-modifiable health factors
Targets:	Absence of stroke in comparison with stroke group

1.1.1.3. Primary Prevention: Use case 3

Aim:	Prevention of stroke
Target population:	General population at risk of stroke
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Reduction of risk factors and increase of health factors by mobile application **based on machine learning and/or hybrid modelling tools**
Success measure:	Reduction of occurence of stroke, increased understanding and compliance.
Features:	Modifiable and un-modifiable risk factors
Targets:	Prediction of stroke risk within x years, prediction of risk-factors/compliance

1.1.2 Stroke Secondary Prevention

In the stroke secondary prevention scenario both potential intervention options as well as input parameters change. On one hand it is shown that pharmacological treatment is necessary to prevent another cerebrovascular event[8]. On the other hand the first cerebrovascular episode, TIA or stroke, will normally lead to performance of tests, the results of which will generally be available for predictive models. Amongst them the most important is neuroimaging diagnostics as well as specialized tests to determine stroke etiology. Also the number of prior events will be predictive of future events. This will modify the input parameters for predictive models.

1.1.2.1. Secondary Prevention: Use case 1

Aim:	Prevention of another stroke event
Target population:	High risk population after first stroke event (TIA or stroke)
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Reduction of risk factors / Medication / Surgery
Success measure:	Reduction of occurence of re-stroke
Features:	Modifiable and non-modifiable risk factors
Targets:	Prediction of stroke risk within x years, prediction of risk-factors/compliance

1.1.2.2. Secondary Prevention: Use case 2

Aim:	Prevention of another stroke event
Target population:	High risk population after first stroke event (TIA or stroke)
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Increase of health factors to reduce re-stroke risk
Success measure:	Reduction of reoccurence of stroke
Features:	Modifiable and non-modifiable health factors
Targets:	Absence of re-stroke in comparison with re-stroke group

1.1.2.3. Secondary Prevention: Use case 3

Aim:	Prevention of another stroke event
Target population:	High risk population after first stroke event (TIA or stroke)
Identification by:	Health care professional
Location:	Out-patient setting
Intervention:	Reduction of risk factors and increase of health factors by mobile application **based on machine learning and/or hybrid modelling tools**
Success measure:	Reduction of reoccurence of stroke, and increased understanding by patient and increased patient compliance to treatment
Features:	Modifiable and non-modifiable risk factors
Targets:	Prediction of stroke risk within x years, prediction of risk-factors/compliance

1.2 Acute Stroke Treatment

There have been advances in the therapy of ischemic stroke in the past decades. Overall therapy success, however, is still poor. For thromboembolic stroke, the most favourable current treatment paradigm is the time-based dissolution of the obstructing blood clot by a drug or its mechanical removal. Unfortunately, up to 20% of patients arrive with an unknown time from stroke onset, and most patients present too late in the hospital to receive treatment. Also, only very few patients are eligible for mechanical thrombectomy [9], whereas the number needed to treat for intravenous thrombolysis drastically increases with time and reaches around 10 in the time window where most patients are treated (Hacke et al. 2008). Latest results have shown that the so called DWI-FLAIR-mismatch, a mismatch of stroke related signals in two different MRI-sequences, can identify patients eligible for treatment independent of their onset time[10].

Approaches like these are called "tissue-based" approaches which have a much higher potential for patient selection than the purely time-based approaches of the past. However, they are not widespread and the DWI-FLAIR mismatch – as the only validated one – relies on MR-imaging which is far less often used than CT-imaging in the acute setting.

For this topic the adjustment of the use cases will be relatively major. The advent of mechanical thrombectomy and its continuous success has considerably changed the treatment schemas for acute stroke patients. On the other hand, still quite some uncertainty exists in which patients the new treatment methods can be applied. Here, national and international guidelines currently are updated regularly.

The main adjustment regarding use cases are triggered by the more complex stroke treatment setting. Neurologists are increasingly interested in a more fine-grained approach to treatment. The current functional outcome paradigm - the mRS score after 3M - does not capture existing more subtle differences between patients. Here, short-term functional QoL outcome might better describe the direct therapy success. A main contribution of the P4Q consortium will be the adaptation to the current clinical changes and the redefinition of use cases with potential new targets which will be validated in the acute stroke study in WP5. Also, imaging based prediction of stroke progression is added here as additional use-case that might give better visual guidance regarding treatment success in contrast to the simple numbers the other models will provide.

1.2.1 Acute Treatment: Use case 1

Aim:	Treatment selection for stroke patients
Target population:	Patients with acute stroke
Identification by:	ER-staff
Location:	acute care hospital, ER
Intervention:	stroke treatment
Success measure:	QoL measure describing therapy success
Features:	Clinical features, Neuroimaging, mechanistic models
Targets:	3 months mRS (classic QoL functional outcome parameter)

1.2.2 Acute Treatment: Use case 2

Aim:	Treatment selection for stroke patients
Target population:	Patients with acute stroke
Identification by:	ER-staff
Location:	acute care hospital, ER
Intervention:	stroke treatment
Success measure:	QoL measure describing therapy success
Features:	Clinical features, Neuroimaging, mechanistic models
Targets:	discharge NIHSS (classic QoL functional outcome parameter)

1.2.3 Acute Treatment: Use case 3

Aim:	Treatment selection for stroke patients
Target population:	Patients with acute stroke
Identification by:	ER-staff
Location:	acute care hospital, ER
Intervention:	stroke treatment
Success measure:	QoL measure describing therapy success
Features:	Clinical features, Neuroimaging, mechanistic models
Targets:	novel short term QoL marker treatment adjusted

1.2.4 Acute Treatment: Use case 4

Aim:	Treatment selection for stroke patients
Target population:	Patients with acute stroke
Identification by:	ER-staff
Location:	acute care hospital, ER
Intervention:	stroke treatment
Success measure:	QoL measure describing therapy success
Features:	Clinical features, Neuroimaging, mechanistic models
Targets:	novel long term QoL marker treatment adjusted

1.2.5 Acute Treatment: Use case 5

Aim:	Treatment selection for stroke patients
Target population:	Patients with acute stroke
Identification by:	ER-staff
Location:	acute care hospital, ER
Intervention:	stroke treatment
Success measure:	Reduction in stroke size
Features:	Clinical features, Neuroimaging, mechanistic models
Targets:	stroke lesion volume

1.3 Stroke Rehabilitation

Medical complications are an important problem in stroke rehabilitation phase and present potential barriers to optimal recovery. Several previous studies have suggested that complications not only are common, with estimates of frequency ranging from 40% to 96% of patients, but also are related to poor outcome[11]. Many of the complications described are potentially preventable or treatable if recognized.

1.3.1 Stroke Rehabilitation: Use case 1

Aim:	Medical complications prevention
Target population:	Subacute stroke patients
Identification by:	Medical doctor, nurse
Location:	Rehabilitation care hospital
Intervention:	Stroke inpatient rehabilitation
Success measure:	Reduction in medical complications
Features:	Clinical assessments , tests, controls, analysis, predictive models, ICD codes
Targets:	Prediction of possible medical complications

Spasticity is a common, but not an inevitable condition, in patients with stroke. Spasticity following stroke is often associated with pain, soft tissue stiffness, and joint contracture, and may lead to abnormal limb posture, decreased quality of life, increased treatment cost, and increased caregiver burden[12].

Early detection and management of post-stroke spasticity may not only reduce these complications, but may also improve function and increase independency in patients with spasticity.

There are no large studies on the natural history of spasticity and contracture development, but permanent loss of joint range has been reported to occur within 3-6 weeks after stroke[13].

There are several approaches to control spasticity, including non-pharmacological and pharmacological treatments, and are usually combined in clinical practice. The goal of spasticity management is to avoid complications, and to increase functional abilities and improve the quality of life.

1.3.2 Stroke Rehabilitation: Use case 2

Aim:	Spasticity treatment management in subacute stroke
Target population:	Subacute stroke patients
Identification by:	Medical doctor, nurse, physiotherapist

Location:	Rehabilitation care hospital
Intervention:	Stroke inpatient rehabilitation
Success measure:	Reduction in medical complications
Features:	Clinical assessments , muscle tone, analysis, predictive models, paresis
Targets:	Prediction of spasticity levels (MAS Scale and the Modified Tardieu Scale)

Literature from the last two decades points to stroke as an important cause of cognitive decline and dementia. Cognitive impairments following stroke may prohibit survivors from being independent in activities of daily living and is associated with poor long-term outcome with higher disability and greater institutionalization rates. While stroke remains a prominent cause of morbidity, the age-standardized rates of mortality seem to decrease worldwide, while the number of strokes each year still increases. As the number of survivors with functional and cognitive impairments must be rising, so is the interest in finding good cognitive outcome predictors and rehabilitation options.

A typical cognitive rehabilitation program mainly provides tasks which require repetitive use of the impaired cognitive system in a progressively more demanding sequence of tasks. The rehabilitating impact of a task depends on the ratio between the skills of the treated patient and the challenges involved in the execution of the task itself. Thus, determining the correct training schedule requires a quite precise trade-off between sufficient stimulation and sufficiently achievable tasks, which is far from intuition, and is still an open issue, both empirically and theoretically[14]. It is difficult to identify this maximum effective level of stimulation and therapists use their expertise in daily practice,without precise guidelines on these issues. A standard cognitive rehabilitation treatment takes 2-5 months distributed in 3-5 sessions a week, each session is composed of 5-10 cognitive rehabilitation tasks. Typically each patient executes a different number of tasks along treatment and in a different order.

Approximately one third of patients who survive the acute phase after stroke are aphasic. Aphasia due to stroke is associated with increased mortality, worse functional recovery, and lower chances of returning to work activities[15]. Therefore we consider specific use cases on aphasic subacute rehabilitation.

1.3.3 Stroke Rehabilitation: Use case 3

Aim:	Cognitive rehabilitation treatment selection for non-aphasic stroke patients
Target population:	Subacute stroke non-aphasic patients
Identification by:	Neuropsychologist
Location:	Rehabilitation care hospital
Intervention:	Cognitive rehabilitation for non aphasic stroke patients
Success measure:	Reduction of level of non-compliance along treatment
Features:	Attention, memory executive functioning assessment, predictive models
Targets:	Prediction of level of compliance by cognitive function, session or treatment

1.3.4 Stroke Rehabilitation: Use case 4

Aim:	Cognitive rehabilitation treatment selection for aphasic stroke patients
Target population:	Subacute stroke aphasic patients
Identification by:	Neuropsychologist, Speech therapist
Location:	Rehabilitation care hospital
Intervention:	Cognitive rehabilitation for aphasic stroke patients
Success measure:	Reduction of level of non-compliance along treatment
Features:	Denomination, repetition, writing, reading assessment, predictive models
Targets:	Prediction of level of compliance by cognitive function, session or treatment

1.3.5 Stroke Rehabilitation: Use case 5

Aim:	Cognitive rehabilitation treatment selection for non-aphasic stroke patients
Target population:	Subacute stroke non-aphasic patients
Identification by:	Neuropsychologist
Location:	Rehabilitation care hospital
Intervention:	Cognitive rehabilitation for non aphasic stroke patients
Success measure:	Improvement in cognitive functions involved in main ADLs activities
Features:	Attention, memory executive functioning assessment, predictive models
Targets:	Prediction of NRR at task level, by cognitive functions and time frames

1.3.6 Stroke Rehabilitation: Use case 6

Aim:	Cognitive rehabilitation treatment selection for aphasic stroke patients
Target population:	Subacute stroke aphasic patients
Identification by:	Neuropsychologist, Speech therapist
Location:	Rehabilitation care hospital
Intervention:	Cognitive rehabilitation for aphasic stroke patients
Success measure:	Improvement in speech cognitive functions
Features:	Denomination, repetition, writing, reading assessment, predictive models
Targets:	Prediction of NRR at task level, by speech functions and time frames

1.4 Stroke Reintegration

While the majority of stroke survivors return to live in the community, re-integration may be an enormous challenge. The ability to return to an acceptable lifestyle, participating in both social and domestic activities is important for perceived quality of life. The present section addresses use cases arising following discharge from hospital care or rehabilitation into the community. These include social support, impact of caregiving on informal carers, family functioning, provision of information and education, leisure activities and return to work.

Every stroke patient, after discharge from Institut Guttmann, periodically undergoes follow up evaluations which may also lead to detect early pathology that, due to the characteristics of the specific lesion, could be asymptomatic and/or remain unnoticed until advanced stages.

Therefore such evaluations are preventive actions, which aim to reduce the incidence of complications in the population with acquired brain damage while allowing the monitoring of the results of long-term treatment, in terms of restriction of participation, as well as the assessment of the family, community and employment insertion.

It has a periodicity of 12-24 months, patients can request it by telephone, or in person to the Admissions Service, which, approximately one month before the evaluation, sends a reminder letter of the visit to the patient by mail. The periodic review will be done within the least amount of time as possible, with the objective of interfering as little as possible in the usual activities of the person (it usually takes from 9:00 to 12:30 during one morning). There is also the possibility, for patients from other Autonomous Communities of Spain or abroad, to perform this procedure within a short admission to the hospital of less than 5 days.

Subsequently, within approximately three weeks, the patient receives at home the report with the conclusions of the medical examinations. If problems have been detected that require urgent intervention, patients will be personally contacted or the responsible relative, to give the pertinent information as well as to request additional tests or refer to the adequate service for the follow-up and / or treatment of the eventual complications detected.

1.4.1 Stroke Reintegration: Use case 1

Aim:	Functional independence in motor activities in chronic stroke patients
Target population:	Chronic stroke patients
Identification by:	Psychologist, Social worker, physiotherapist, nurse
Location:	Rehabilitation care hospital
Intervention:	Functional rehabilitation for chronic stroke patients
Success measure:	Reduction of dependency levels in ADLs
Features:	Transfers, locomotion, social cognition, self-care activities
Targets:	Prediction of level of independence (FIM, BI) in ADLs within x years

1.4.2 Stroke Reintegration: Use case 2

Aim:	Community integration in chronic stroke patients
Target population:	Chronic stroke patients
Identification by:	Psychologist, Social worker, physiotherapist, nurse
Location:	Rehabilitation care hospital
Intervention:	Functional rehabilitation for chronic stroke patients
Success measure:	Productive activities, social integration
Features:	Home, social interactions, productive activities, work, school, leisure
Targets:	Prediction of level of community integration (CIQ) within x years

1.4.3 Stroke Reintegration: Use case 3

Aim:	Identify fragility trajectories along time in chronic stroke patients
Target population:	Chronic stroke patients
Identification by:	Psychologist, Social worker, physiotherapist, nurse
Location:	Rehabilitation care hospital, home setting
Intervention:	Rehabilitation for chronic stroke patients - community integration
Success measure:	Decreasing trajectory levels along time
Features:	Home, social interactions, productive activities, work, school, leisure
Targets:	Prediction of trajectory levels (PCRS, CIQ, ESIG questionnaries) within x years

1.4.4 Stroke Reintegration: Use case 4

Aim:	Overload levels in informal caregivers of chronic stroke patients
Target population:	Chronic stroke patients and informal caregivers
Identification by:	Psychologist, Social worker
Location:	Rehabilitation care hospital and home settings
Intervention:	Rehabilitation for chronic stroke patients - community integration
Success measure:	Reduction in overload level in informal caregivers
Features:	Home setting, social interactions, caregivers' burden
Targets:	Prediction of level of overload (ZARIT Overload scale) within x years

2 Risk, Health and Resilience Factors

In many machine learning based AI applications of the (recent) past the focus of the models was to predict disease based on risk-factors. A more holistic approach expands this view by focusing not only on disease and risk, but also on health and health-factors as well factors that lead to resilience towards disease. The neglected question why a patient stays healthy is equally important to the questions why they get sick, and why some recover well and why some do not, and that question is therefore also going to be addressed by PRECISE4Q. For this purpose, We will develop multi-scale predictive patient-specific models that will explore disease prevention, treatment and rehabilitation in stroke. These models are specifically designed to not only explore risk factors, but also health factors. For this purpose, our outcome parameters will centre around a quality-of-life concept to define wellbeing. Here, we will distinguish between:

- Risk factors: Factors increasing the risk of a negative outcome (e.g. stroke occurrence, bad outcome after stroke)
- Health factors: Factors decreasing the risk of a negative outcome (here, independent factors are meant, not absence of risk factors)
- Resilience factors: Factors that help recovery when a negative outcome occurred.

2.1 Risk factors

According to the WHO, risk factors are defined as: "A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury." In contrast, however, Hollnagel points out that - from an epidemiological point of view - risk factors are factors that predict the disease[16]. Thus, risk factors are associated with the disease, but are not necessarily causal for development of the disease. This is easy to highlight by a factor like "age". Age will be a good predictor for many diseases, since an 80-year-old is less likely to contract measles in contrast to an 8-year old. However, age did not causally contribute to the 8 year old contracting measles.

Thus, for the P4Q project we will follow the epidemiological definition and we will thus expand the WHO definition as follows:
"A risk factor is any attribute, characteristic or exposure of an individual that **is associated with a higher** likelihood of developing a disease or injury."

This is highly important when the goal is not only to find new associations, but also to develop interventions to prevent the disease. Depending on causality, avoidance of a risk factor may or may not lead to lower incidence of the disease[16]. Also, influencing one parameter - even if causal - does not necessarily lead to decreased incidence, when the genesis of the disease is multifactorial and risk factors influence each other[16]. Thus, interventions must be confirmed by a) shown association, b) theoretical understanding and c) longitudinal intervention studies. Thus, it is possible to use the reduction of a risk factor as a surrogate end point for a study, but only if the direct causal relationship between the risk factor and the outcome is established with high scientific certainty[16].

In contrast to epidemiology which is concerned with groups, machine learning allows for personalized predictions of risk. However, the above considerations hold true for machine learning based approaches as well. We need to keep in mind that the models developed in P4Q are exploratory scientific findings establishing new associations between features and outcome. These findings need to be included into a theoretical explanatory framework and new interventions studies need to be planned based on our results. However, the new machine learning models will allow for the first time to test personalized interventions in contrast to the general recommendations of the past.

A related concept to these three is called vulnerability[17,18]. It is a concept that is related to the concept of frailty, even though frailty is mostly used in connection to elderly. A vulnerable person can be of any age, and the defining feature is that such a person is more likely to suffer from a disease, such as a stroke. Factors that contribute to vulnerability include both socioeconomic and sociopsychological factors, and more physiological factors. It is for instance well established that people with a lower income, with a lower education level, or with a smaller social network have several years shorter life expectancy, and are almost 3 times as likely to suffer a cardiovascular event, compared to those with high scores in those corresponding factors[19]. One of the things that we will explore in the hybrid modelling (see D4.4) is how these softer values can be included in the more physiological and mechanistic descriptions of physiology. This work will allow us to bridge the gap from psychosociological factors to such other physiological factors that also contribute to vulnerability. Such more physiological factors includes e.g. a loss of allostasis (measured as cortisol variations during a day or in response to a stress test), vulnerable plaques, inflammation, etc. All in all, the risk, health, and resilience factors cover the same factors as the concept of vulnerability does, and there is therefore in this Deliverable no reason to include a separate list of vulnerability factors.

2.2 Health factors

Hollnagel argues that the strong focus on risk factors has prevented modern medicine to appreciate health factors, i.e. factors that are associated with a decrease of the likelihood to develop a disease[16]. This is immediately evidenced by the fact that no readily available definition of a health factor exists. Here, two possible approaches exists. One one hand, absence of a risk factor can be seen as a health factor. For example, obesity is associated with the likelihood of stroke occurrence, and lack of obesity is associated with lower risk, is thus a health factor. On the other hand, there are factors which are likely independently from a common risk factor associated with lower occurrence. An example would be physical exercise, which might have a protective effect. We can see, however, that the distinction is somewhat arbitrary, since it is possible to define the “lack of exercise” as a risk factor.

We suggest to follow the practical viewpoint that the presence of a factor should determine its allocation to risk or health factors. Or in other words: A GP would not ask a patient: “Are you **not** exercising?” and also not “Do you **not** have diabetes”? They would ask “Are you exercising” and “Do you have diabetes”. Thus exercising would be considered a health factor and diabetes a risk factor.

Therefore the definition:
“A health factor is any attribute, characteristic or exposure of an individual that is associated with a lower likelihood of developing a disease or injury.”

2.3 Resilience factors

Research on resilience has increased substantially over the past two decades and is now also receiving increasing interest from stakeholders involved with policy and practice in relation to its potential impact on health, well-being, and quality of life[20].

One of the greatest challenges in the field of resilience is the variety of definitions of resilience used in research and in practice. It is also the case that researchers often do not define resilience clearly, or indeed at all, and often researchers refer in passing to resilience, but without evidence, or they use it in a lay person's terms[21].

How resilience is **defined** reflects how it might be **measured** and **promoted**, so assessment is intricately tied up with issues of definition. The definitions highlight a number of factors that could be considered defining attributes of resilience (e.g. adversity, resistance, adaptation). However, to understand resilience it is also important to understand what underlies these attributes and the subsequent outcomes.

2.3.1 Definitions

Resilience originates from the Latin 'resilire' (to leap back). General dictionary definitions state that the noun 'resilience' is a derivative of the adjective 'resilient,' which has two uses:

(i) 1. able to recoil or spring back into shape after bending, stretching, or being compressed; 2. (of a person) able to withstand or recover quickly from difficult conditions.

(ii) 1. (of a person) recovering easily and quickly from misfortune or illness; 2. (of an object) capable of regaining its original shape or position after bending or stretching.

Resilience is therefore the ability of an individual to 'bounce back' from adversity. It is considered the strength and courage that individuals draw upon, enabling them to overcome negative circumstances so they can continue on through life. It has been defined by [22] and others[23] as *the ability to overcome or adapt to extreme stress or adversity*.

Resilience has also been viewed as the individual's ability to resist or recover from hardship. Masten, Best and Garmezy (1990) defined resilience as *process, capacity or outcome of successful adaptation despite challenges or threatening circumstances…good outcomes despite high risk status, sustained competence under threat and recovery from trauma.*

Early definitions of resilience included factors such as personal characteristics [24], mechanisms and proc[25], or outcomes that the individual may experience[26]. A large proportion of these early studies examined what protective factors enhanced an individual's resilience[27]. Subsequent studies explored mechanisms and processes whereby interest focused on the pathways that have led to successful adaptation [28,29]. Other propositions that have contributed to the definitions of resilience included the behavioural outcome of adjustment[26].

Overall, the construct of resilience is not easy to capture or measure. Early efforts at clarifying and describing the concept of resilience have led to various approaches in its meaning. This inconsistency with clarifying its meaning has extended into contemporary literature. Greeff and Holtzkamp defined resilience within a family construct[30]. Conversely, Hegney et al. viewed resilience as a combination of individual, group and community factors that enhance psychological wellness in communities[31]. Whereas, Hjemdal et al. considered resilience as the protective factors, processes and mechanisms, that contribute to good outcomes[32].

One of the main tasks of the Resilience and Healthy Ageing Network, funded by the UK Cross-Council programme for Life Long Health and Wellbeing, was to contribute to the debate regarding definition and measurement.

As part of the work programme, the Network examined how resilience could best be defined and measured in order to better inform research, policy and practice. An extensive review of the literature and concept analysis of resilience research adopts the following definition[33]:

Resilience is the process of negotiating, managing and adapting to significant sources of stress or trauma. Assets and resources within the individual, their life and environment facilitate this capacity for adaptation and bouncing back in the face of adversity. Across the life course, the experience of resilience will vary.

This definition, derived from a synthesis of over 270 research articles, provides a useful benchmark for understanding the operationalisation of resilience.

One way of ensuring data quality is to only use resilience measures which have been validated. This requires the measure to undergo a validation procedure, demonstrating that it accurately measures what it aims to do, regardless of who responds (if for all the population),when they respond, and to whom they respond. The validation procedure should establish the range of and reasons for inaccuracies and potential sources of bias. It should also demonstrate that it is well accepted by responders and that items accurately reflect the underlying concepts and theory. Ideally, an independent 'gold standard' should be available when developing the questionnaire.

2.3.2 Measuring Resilience

With the importance of context and intended use in mind, in this section we provide a diverse sample of validated resilience scales. While there are several resilience measures, we narrowed them down to the eight most popular and most empirically based resilience scales. These scales are listed and described below.

2.3.2.1. Connor-Davidson (CD-RISC)

A study conducted by Windle, Bennett, & Noyes reviewed nineteen resilience measures[34]. However, out of nineteen, only three of them received superior psychometric ratings, one of which is the Connor-Davidson Resilience Scale (CD-RISC).
This scale was originally developed by Connor-Davidson as a self-report measure of resilience within the Post Traumatic Stress Disorder (PTSD) clinical community[35]. It is a validated and widely recognized scale with 2, 10, and 25 items which measure resilience as a function of five interrelated components: Personal Competence, Acceptance of Change and Secure Relationships, Trust/Tolerance/Strengthening Effects of Stress, Control and Spiritual Influences.
With an extensive number of studies using this tool, conducted within a varied range of populations, the CD-RISC is considered one of the higher scoring scales in the psychometric evaluation of resilience [34].

2.3.2.2. Resilience Scale for Adults (RSA)

The RSA, another resilience scale rated highly by Windle et al., was authored by Friborg et al. as a self-report scale targeting adults[36]. It is recommended for use in the health and clinical psychology population. This scale has five scoring items which examine both the intrapersonal and interpersonal protective factors that promote adaptation to adversity. The authors noted the key factors which contribute to highly resilient individuals, namely family support and cohesion, external support systems, and dispositional attitudes and behaviours, which the scale items are founded on. They are: Personal Competence, Social Competence, Social Support, Family Coherence and Personal Structure.
A later study performed by Friborg et al. used the RSA to measure the relationship between personality, intelligence, and resilience[37]. They found many links between personality and resilience factors, such as the connection between higher personal competence and elevated emotional stability. There were, however, no significant findings related to cognitive ability.

This is in line with Windle et al., who concluded that the RSA is highly useful for assessing the protective factors which inhibit or provide a buffer against psychological disorders.

2.3.2.3. Brief Resilience Scale (BRS)

While most resilience assessments look into the factors which develop resilience, The Brief Resilience Scale (BRS) is a self-rating questionnaire aimed at measuring an individual's' ability to "bounce back from stress". This instrument, developed by Smith et al. , has not been used in the clinical population; however, it could provide some key insights for individuals with health-related stress[38].
Amat et al. explain that the BRS instrument consists of six items, three positively worded items, and three negatively worded items[39]. All six relate to the individual's ability to bounce back from adversity. The scale's development controlled for protective factors such as social support in order to get a reliable resilience measure[38].

2.3.2.4. Resilience Scale (RS)

This scale dates back to 1993 but is still in use by many researchers. The Resilience Scale, developed by Wagnild and Young in 1993, was created and validated with a sample of older adults (aged 53 to 95 years)[40]. Consists of 25 items and the results have been found to positively correlate with physical health, morale, and life satisfaction, while negatively correlating with depression. The scale is intended to measure resilience based on five essential characteristics: Meaningful Life (or Purpose), Perseverance, Self-Reliance, Equanimity and Existential Aloneness.
These five characteristics are assessed using two subscales, the 17-item Personal Competence subscale and the 8-item Acceptance of Self and Life subscale. Subsequent validation reaffirmed the scale´s internal consistency and construct validity, supporting its continued effectiveness as a tool for the assessment of resilience[41].
In addition to the original 25-item scale, there is a shortened 14-item scale that has also proven to be valid and reliable in measuring resilience[42].

2.3.2.5. Scale of Protective Factors (SPF)

The Scale of Protective Factors (SPF) was developed by Ponce-Garcia, Madewell, and Kennison in 2015 to capture a comprehensive measurement of resilience[43]. The authors tested and validated this resilience scale in a sample of nearly 1,000 college students, and found the SPF to be valid and reliable for measuring resilience, especially in groups identified as survivors of violent trauma.
This scale measures resilience in a slightly different way than the previously mentioned scales. It focuses on the factors that combine to create a buffer between individuals who have experienced trauma and the stress and disruption to functioning that can follow, rather the components that constitute resilience directly.
It consists of 24 items measuring two social-interpersonal factors (and) and two cognitive-individual factors (and). The SPF has since been validated in a review of resilience scales by Madewell and Ponce-Garcia, providing evidence of its validity and effectiveness in clinical use[44]

2.3.2.6. Predictive 6-Factors Resilience Scale (PR6)

The Predictive 6-Factor Resilience Scale was developed based on the neurobiological underpinnings of resilience and the theorized relationship with health hygiene factors[45]. The PR6 measures resilience as a function of six domains concerning several interrelated concepts:

- Vision: self-efficacy and goal-setting

- Composure: emotional regulation and the ability to identify, understand, and act on internal prompts and physical signals
- Tenacity: perseverance and hardiness
- Reasoning: higher cognitive traits, like problem-solving, resourcefulness, and thriving
- Collaboration: psychosocial interaction, such as secure attachment, support networks, context, and humor Health: physiological health

The PR6 was found to have good internal consistency and correlate with other measures of resilience as well as health hygiene scores.

Based on these results, the PR6 can be considered an effective measurement and a particularly good assessment for use in improving resilience

2.3.2.7. Ego Resilience Scale (RS-14)

This scale was developed by Block and Kremen in 1996 for use in measuring resilience in non-psychiatric contexts[46]. While the authors term their construct "ego resiliency," it is basically resilience as we know it viewed in terms of adaptability to changes in one's circumstances.

The Resilience Scale (RS-14) consists of 14 items rated on a scale from 1 = does not apply to 4 = applies very strongly, with higher scores indicating higher levels of resilience.

Scores on this scale have been found to positively correlate with intelligence as it relates to the ability to adapt, supporting the scale's ability to assess an individual's ability to bounce back from failure and disappointment.

2.3.2.8. Academic Resilience Scale (ARS-30)

The Academic Resilience Scale (ARS-30) is a recently developed measure used to assess resilience in a particular context: academic success. Simon Cassidy describes academic resilience as the tendency to persevere and succeed in education despite meeting with adversity[47]. It is a multi-dimensional construct focusing on both cognitive affective and behavioural responses to academic adversity. The ARS-30 is based on responses to a vignette describing a significant academic challenge, rated on a scale from 1 = likely to 5 = unlikely. The items in this scale fall into one of three factors:

- Perseverance
- Reflecting and Adaptive Help-Seeking
- Negative Affect and Emotional Response

High scores on factors 1 and 2 and low scores on factor 3 indicate high resilience. This scale was found to be highly internally reliable, and scores correlated significantly with a measure of academic self-efficacy. While the ARS-30 is most appropriate in academic contexts, scores can be useful in other situations as well

2.4 Why Resilience?

A number of studies have confirmed that the emotional problems encountered following stroke are far from receiving the same attention as the physical and cognitive aspects of recovery[48,49].

In recent years there have been efforts directed at generating knowledge about the negative reactions encountered by stroke survivors and their experiences in recovering from stroke.

Subsequently, the literature has identified a variety of emotions expressed by those suffering from the consequences of stroke. These emotional reactions include frustration, anger, overt sadness, grief, loss, shock, vulnerability and worry[50]. Other emotional reactions that have been known to occur include a sense of hopelessness and helplessness, embarrassment, and feelings of entrapment[51].

Subsequently, it has been well established that the greater the risk and/or adverse experience to the individual, the greater the likelihood that the person will develop maladaptive behaviour[37]. As a result there has been a large amount of work invested into exploring, understanding, and diagnosing maladjusted behaviour with the view of uncovering and applying the most appropriate treatments[52].

Moreover, the literature has recognised that there is a large variation in how individuals respond to life stressors and adversities. We now acknowledge that there are individuals who succumb to maladaptive disorders, whereas others show resilience and manage to adapt to their circumstances and even come through their negative experience strengthened[24].

Not surprisingly, this prompted researchers to explore the appealing effects of the notion of resilience. There has long been the assumption that those who experience adversity or trauma will succumb to the effects of these circumstances and develop disorders. As noted by Glicken we tend to think that traumas will lead to malfunctioning behaviour, but often this is not the case[53]. There is a developing research awareness of situations where people who are suffering from a serious illness are able to draw upon selective strengths and assets to help them combat the negative effects of illness.

Understanding resilience and its buffering effects during stroke recovery has only been recently tackled. In a qualitative study conducted in the Philippines, deGuzman et al. had nine elderly post stroke participants with residual paralysis complete a cartographic sketch, semi-structured interviews and a mask-painting activity to describe self-concept, disposition, and resilience post stroke[54]. While there were certain consistencies absent in the methodological design, the findings revealed a number of themes that emerged from the data. Self-concept was represented by relationality and corporeality. Rationality is how people connect, interact, and find meaning with the bonds they build with others. Corporeality is the quality of being physical and material in nature – an individual's perception of self through his/her attributes. Disposition was described as phylogenetic and ontogenetic, that is, phylogenetic is the mood or temperament shown by the respondents originate (pre-stroke) from the situation or events happening in their lives. Whereas, ontogenetic is the respondents' (post-stroke) behaviours and personalities as shown because they are who they really are. In addition to these findings Guzman et al. also noted resilience was categorised under two origins: conviction and condition. Conviction was viewed as the strong persuasion or fixed belief incurred during youth. Condition was perceived as the respondents' ability to bounce back and cope after the diagnosis of stroke.

There are stroke survivors who managed to adapt to their altered circumstances despite adversity. These individuals demonstrated patterns of behaviour which underscored features of resilience. They were able to draw upon essential resources and strengths that promoted positive adaptation and ameliorated any stressful circumstances.

Features of resilient individuals included having a positive outlook on life, setting goals for the future, having a vast amount of friends, an ability to develop friendship networks, and pursuing social engagements and activities.

2.5 Resilience factors

This section presents an account of factors most prevalent in individuals that were identified in stroke survivors as incorporating resilient enhancing qualities[55]. Individuals who demonstrated these resilient elements in their recovery appeared to successfully manage adjustment and reintegration back into the community, as well as improve their sense of well-being. Factors most prominently utilised included: Individual disposition, competence, self–esteem, and social support. In addition, it is highlighted that the presence of intrapersonal elements also plays a key role in the participant's ability to renegotiate their lives following stroke.

2.5.1 Individual disposition

Individual disposition is highlighted by maintaining a sense of hope, optimism and the ability to remain confident throughout their recovery. Optimistic individuals made plans, spoke about their hard work and considered themselves lucky even in the face of adversity. Participants displaying optimistic tendencies approached challenges with confidence and viewed the source of their success as determined by self. Plans were made for the future and this was discussed with partners and family members. Hope was the element that enabled participants to strive towards an expected goal or outcome. Belief in their ability to obtain a goal meant participants acted, moved, progressed, and made changes, thereby influencing the attainment of something they desired.

2.5.2 Competence

Experiencing a sense of competence in tasks and/or activities appeared to nurture the participants' self-assurance and autonomy. Attempting to carry out, and complete activities, meant a great deal. Furthermore, ingrained within the stroke survivors sense of confidence was self-efficacy and their ability to problem-solve. They believed in their own ability to control and cope with challenges as well as in dealing with stress. There were expectations of successfully performing or negotiating particular tasks and a sense of self-regulation of their abilities. Rather than avoid difficult tasks, they instead considered various options and solutions. They confidently engaged in effective planning strategies, and adjusted their abilities in regards to their circumstances.

2.5.3 Self-esteem

A high sense of self-esteem appeared to permeate into most areas of these participants' lives. They were more likely to pursue goals, achieve tasks, seeks new friends, develop ongoing networks, engage in diverse social activities and have confidence in their abilities. They valued both positive and critical feedback from others. Having this positive sense of self appeared to underpin their ability to face challenges and deal with negative feedback effectively. Participants often demonstrated their sense of self-esteem in their ability to connect and socialise with others.

2.5.4 Social support

Social support was viewed as a crucial factor in enabling participants to successfully renegotiate their lives. The various types of support (practical and emotional) assisted in alleviating some of the multiple issues and concerns faced by individuals in their adjustment after stroke. Practical support included tangible supports such as exercise programs, home care, transport, financial assistance and vocational assistance. Emotional support was conveyed through the means of a confidante, those who listened, and the support offered by others that was not of a practical nature.

2.5.5 Emotional support

Emotional support was a pivotal element in the successful adjustment of these participants. This type of support was conveyed through the means of a confidante, those who listened, and the support offered by others that was not of a practical nature. This support increased and strengthened during the critical period post stroke, and appeared to taper off later in the recovery process. Even though the support offered tapered off following the acute period after stroke, it did not terminate completely. Moreover, this support was readily accessible when the participant's required it.

2.5.6 Intrapersonal factors

A number of additional themes from the interviews were featured and categorised under intrapersonal factors. These were additional attributes present within the individual that appeared to also play a key role in the participant's ability to successfully renegotiate their lives following stroke. Themes included motivation, determination, perseverance, personal philosophy, and humour.

Motivation

Participants viewed their motivation as a source of ongoing energy. Several participants appeared to have powerful intrinsic impulses and drives that enabled them to perform and address unmet needs. For instance, these participants were not satisfied with a reduced network of friends, or limiting their social outings, or working within the boundaries of a set exercise program; they were motivated and driven.

Determination

As noted by Glicken (2006), determination provides individuals with the positive notion they are able to master most life situations. It is a mindset. Determination was a cognitive reflection that led to behavioural actions. Determination is what was drawn upon that allowed several participants to complete tasks and resolve issues. Not only did the participants think about and consider the notion of determination, but they also put this into action allowing it to drive their desire to recover at an optimal level.

Perseverance

Perseverance and persistence appeared to be the key in their ability to keep striving for change. These themes were accentuated when various participants continued to work on difficult tasks without giving up. Even when the challenges appeared too daunting to overcome, participants drew on their strength to keep going and pushed themselves beyond their personal boundaries in the effort to make change. Perseverance was evident when participants pursued answers to difficult questions; or when they worked on physical impairments; or were trying to adapt to their altered lifestyle.

Personal philosophy

Participants also expressed a sense of personal philosophy in dealing with adversity and life in general. These participants often reiterated statements to themselves that appeared to boost their spirits and determination throughout their recovery. Often these affirmations were focused on positive reminders or personal rewards in the efforts of assisting others. For example, 'by assisting others your life is much easier'. Participants commented that their affirmations included statements like, 'live life to the fullest, 'I've got to keep moving, or 'it was either do it, or be fucking miserable'. It was important for participants to stick with their personal philosophy, as it appeared to drive their progress in recovery. One man sums up his personal philosophy regarding his adversity.

Humour

Finally, having a sense of humour appeared to have a positive impact on the stroke survivors otherwise traumatic and unpleasant experience. Several participants engaged in and often dealt with difficult or embarrassing situations by making light of the situation and/or engaging in humorous undertones and suggestions. Sense of humour appeared to provide the participant with strength and meaning in dealing with a variety of situation. Participants who adopted psychosocial factors in combating adversity conveyed the value of intrinsic or intra-personal elements in their adjustment from stroke. These were considered additional and useful tools in overcoming the various day-to-day obstacles. Furthermore, participants viewed these supplementary intrinsic elements as powerful strategies in negotiating their way through life.

2.6 Use case: Back on track intervention

The role of resilience in adjustment after stroke has been little investigated. In this section we present a recent publication on the development and preliminary evaluation of a novel intervention to promote resilience after stroke[56]. They applied the first two phases of the revised UK Medical Research Council (UKMRC) framework for the development and evaluation of complex interventions: intervention development (phase 1) and feasibility testing (phase 2). Methods involved reviewing existing evidence and theory, interviews with 22 older stroke survivors and 5 carers, and focus groups and interviews with 38 professionals to investigate their understandings of resilience and its role in adjustment after stroke. They used stakeholder consultation to co-design the intervention and returned to the literature to develop its theoretical foundations. Results present a 6-week group-based peer support intervention to promote resilience after stroke. Theoretical mechanisms of peer support targeted were social learning, meaning-making, helping others and social comparison. Preliminary evaluation with 11 older stroke survivors in a local community setting found that it was feasible to deliver the intervention, and acceptable to stroke survivors, peer facilitators, and professionals in stroke care and research. This study demonstrates the application of the revised UKMRC framework to systematically develop an empirically and theoretically robust intervention to promote resilience after stroke.

2.7 Resilience as predictor of Quality of Life

Scarce evidence can be found on predictive models specifically linking resilience to QoL in stroke, but related publications in cancer are presented in this section because of their proximity regarding selected variables and proposed analysis methodologies. Although much research has shown that a relationship exists between QoL and resilience in cancer patients[57–60], limited information is available on the nature of this relationship and the degree of the influence of resilience on QoL. Exploring whether resilience is an independent predictor of QoL and estimating the degree of its impact on QoL can help to understand the role of resilience in improving the QoL of cancer (and similarly stroke) patients, as well as provide clinical staff with information on psychological intervention and psychological care programs. In a publication by Tian and Hong publication, the resilience of patients was measured (by means of RS-14 presented in section 4.2.7) prior to treatment, and their psychological distress, fatigue status, and treatment side effects were assessed 3 weeks after[61]. Their QoL was measured after their treatment ended. A relationship model of these variables was

constructed using path analysis. In total, 970 participants, including 699 (72.06%) males and 271 (27.94%) females at an average age of 56.38 years (SD = 12.91), were included in this study. Resilience explained 33.2% of the variance in psychological distress, 16.1% of the variance in fatigue, and 1.23% of the variance in side effects. The relationship between resilience and QoL was statistically significant (β = 0.119, t = 4.499, P < 0.001) when psychological distress, fatigue, and side effects were absent from the regression model, whereas the adjusted regression coefficient of resilience was not statistically significant (t = 1.562, P > 0.05) when these variables were added. Psychological distress, together with fatigue and side effects, could explain 52.40% of the variance in QoL (P < 0.05). Physiological distress accounted for 28.94% of the total effect on QoL, fatigue accounted for 33.72%, side effects accounted for 22.53%, and resilience accounted for 14.80%.
The study concludes that resilience is not an independent predictor of QoL in patients with digestive cancer, but it is a main factor influencing psychological distress and side effects.

In a recent publication, Temprado Albalat and colleagues studied the relationship between resilience and QoL factors (QoL and HRQoL) in patients with a drainage enterostomy[62]. The objective of the research was to analyse the impact of a chronic process, as is the case of a drainage enterostomy, on the HRQoL of these patients and to determine whether resilience has some kind of positive or negative relationship with it. Similarly, it also intends to analyse what types of clinical or sociodemographic variables have some kind of influence upon it. The initial sample consisted of a total of 185 patients who had had a drainage enterostomy for more than 3 months. After applying the inclusion criteria, the final sample included in the study consisted of 125 patients (n = 64 males and n = 36 females).Resilience was measured by means of the Spanish version of the Connor–Davidson Resilience Scale (CD-RISC), presented in section 4.2.1. When performing the multiple linear regression, following the stepwise method, a significant regression equation was obtained in which the predictive variables were resilience and the presence of stoma-related complications. Hence, the higher resilience (main predicting factor) and the lower the percentage of complications (second predictive factor), the higher the verall score on specific HRQoL will be in patients who have undergone an enterostomy. This regression model predicts a variance of 24.4% with both variables. In one-factor ANOVA models, this factor would have to account for at least 10% of the variance of the dependent variable for the factor for it to be considered as having clinical relevance; a value of around 0.25 (25% of the explained variance) would indicate a high or clinically very relevant magnitude. Given these indications, authors conclude that the obtained regression model has very high clinical relevance in explaining the HRQoL of patients who have undergone an enterostomy.

3 Features for each stroke phase and use case

In this section we will outline the features that have been identified in literature research, in previous deliverables and the interdisciplinary consortium work so far that will serve as a basis for the predictive modelling efforts in P4Q. For each stroke phase, features, a short description and their connection to the defined use cases is given. Our overview will be inclusive, i.e. giving an overview of possible features, even if the feature might not be available in the databases available for this project.

3.1 Stroke Prevention

Risk factors for primary stroke can be divided into modifiable and non-modifiable risk factors. While both are crucial for building predictive models, the distinction is very important, since modifiable risk factors allow the development of interventions. Only by specific and individualized interventions strategies can the ultimate goal of PRECISE4Q, a reduction in the incidence of stroke be achieved.

3.1.1Risk factors

3.1.1.1. Age

Age is a main risk factor of stroke. However, while stroke is known to occur with high frequency in the elderly (>65 years) - the mean age at stroke being 69.2 years[63]- latest analyses show that stroke occurrence is increasing in the young population [64]. In extrapolation, by 2025 more than 1.5 million strokes are expected to occur in Europe each year, increasingly targeting younger people[64].

Category: unmodifiable

3.1.1.2. Sex

Sex is known to play a role in the pathophysiology and in the phenotype of stroke. With regards to stroke occurrence, men are generally heavily favoured (m/f ratio=1.33), however, in mid-life and above the age 85 year, stroke is more common in women[65]. However, even though the incidence favors men, due to their higher life-span, more strokes occur in women than in men[66]. Higher stroke risks in mid-life and younger populations for women can be explained by risks related to pregnancy and the post-partum state, as well as other hormonal factors, such as use of hormonal contraceptives[63]. In terms of stroke mortality, stroke mortality is lower in women until the age of 65, whereas in the age group above 65 the mortality of women is higher[65].

Category: unmodifiable

3.1.1.3. Ethnicity

Disparities owing to ethnical differences are well reported in the literature. Increased risk for stroke has been reported for African Americans, Latino Americans and American Indians[63]. However, it is important to mention that these correlations might not not be fully causal, but at least partially due to bias. Here, a higher incidence of stroke related risk factors for minorities has been reported[63]. Thus, socio-economic reasons might be a main driving force behind the reported ethnical differences.

Category: unmodifiable for genetic differences / modifiable for socio-economic differences

3.1.1.4. Family history/genetic Factors

Genetic factors play an important role in the development of stroke, as shown by partial heritability (30% risk increase due to family history), but are challenging to identify and quantify due to high heterogeneity of stroke causes and populations[63]. One can distinguish between single gene disorders, where stroke is the primary or important manifestation of the diseases and genetic variants associated with ischemic stroke. The former include diseases like CADASIL, CARASIL, sickle cell disease, Fabry disease and others[63]. Regarding the latter, few works have explored associations; however, several reports have shown associations between stroke and the ABO blood type gene; Other gene loci were also identified, but here the disease mechanisms are unclear and are a focus of investigation[63].

Category: unmodifiable for genetic differences

3.1.1.5. High blood pressure / Hypertension

Hypertension leads to increased risk of stroke and the incidence of hypertension increases with age[67]. Thus, treatment of hypertension is an effective measure to reduce stroke risk. However, hypertension treatment is still far from optimal in developed countries and low-income countries have the highest prevalence of elevated blood pressure (http://www.who.int/features/qa/82/en/). Recent new strategies are looking into novel ways to assess this biomarker. For example, the variability in blood pressure measurements over time may be a better predictor of risk than the static snap-shot measurements done today[68].

Category: modifiable by life-style and medication

3.1.1.6. Diabetes

Diabetes is an independent strong risk factor for stroke and stroke accounts for 20% of deaths in diabetics[63]. The increase in diabetes prevalence in the younger populations might be explanatory for the overall increasing incidence of stroke in younger people[69].

Category: modifiable by life-style change and medication

3.1.1.7. Smoking

Cigarette smoking is a well known independent risk factor for ischemic stroke, with a dose-response relationship between pack-years and and stroke risk[70].

Category: modifiable by life-style change

3.1.1.8. Carotid artery disease

Another modifiable risk factor is large vessel atherosclerotic disease, mostly presenting as stenosis of the internal carotid artery. It was shown that in asymptomatic with greater than 60% carotid stenosis and low perioperative risk, carotid endarterectomy (CEA) is protective of stroke[63]. Novel therapies try to focus less on the lumen width, but on functional imaging to determine plaque vulnerability, which might be a much better dynamic predictor of stroke risk[71].

Category: modifiable by life-style change, medication and surgery

3.1.1.9. Atrial fibrillation

Atrial fibrillation is one of the largest risk factors for stroke. The current model of blood clot generation due to the stasis of blood in the left atrium is currently challenged, however, leading to the need for new models for the relation of atrial fibrillation and stroke[63]. Nonwithstanding, the treatment of atrial fibrillation can substantially reduce the risk for stroke. Under-treatment of atrial fibrillation is currently still a major public health problem, both in developed[72] and developing countries[73].

Category: modifiable by medication and surgery

3.1.1.10. Dyslipidemia

Changes in the levels of biolipids (mainly cholesterol and triglycerides) are directly associated with stroke incidence. Total cholesterol is associated with higher stroke risk[63]. Higher LDL levels increase the risk of ischemic stroke. Low HDL levels might also be associated with stroke[74]. The relationship of lipids to ischemic stroke, however, varies by stroke subtype, with associations strongest for atherosclerotic subtypes[75]. Study data, whether LDL-lowering interventions have a protective effect are conflicting. For a comprehensive overview, see Boehme et al[63].

Category: modifiable by life-style-change and medication

3.1.1.11. Obesity

Obesity is a risk factor of stroke. However, obesity is a composite parameter with associations to other risk factors. It was shown that 76% of the body-mass-index (BMI) - a common parameter to measure obesity - was explained by blood pressure, cholesterol and glucose levels and blood pressure alone explained 65%[63]. Additionally, the disadvantages of the BMI as a parameter have been increasingly discussed, the waist-to-hip-ratio being a better parameter to predict stroke risk. Better established is the combination of elevated lipids in combination with obesity, pre-hypertension and pre-diabetes coined metabolic syndrome. Here, the combination of several stroke-related risks lead to a generally elevated stroke risk[76].

Category: modifiable by life-style-change, medication and surgery

3.1.1.12. Alcohol intake/Substance abuse

Alcohol abuse and other substances such as cocaine, heroin, amphetamines and others are associated with increased risk of stroke, especially in younger patients[77]. With alcohol, however, a J-shaped association was suggested, where light-to-moderate alcohol consumption might be protective against stroke and only heavy drinking leads to stroke. Here, associations between heavy drinking and hypertension might play a role[63].

Category: modifiable by life-style-change

3.1.1.13. (Cardio)-vascular disease

It is well established that (cardio-)vascular disease is a risk-factor for stroke. Peripheral artery disease (PAD)[78], myocardial infarction and vascular diseases in other body territories increase the risk of stroke[63]. But also heart failure was shown to be associated with stroke risk[79].

Category: partially modifiable by life-style-change

3.1.1.14. Stress

Psychosocial stress has been linked to increased stroke risk[7]. This was also shown in other studies[80]. Potential pathways for causal connections are direct biological effects through stress hormones as well as social effects through lowered compliance and less healthy life styles[80].

Category: partially modifiable by life-style-change

3.1.1.15. Depression

Depression is linked with a significant increase of stroke incidence[81] and was also found to be one the 10 risk factors of the INTERSTROKE study (O´Donnel et al, 2010). Social isolation was also found to be a predictor of stroke, however, most likely through the pathway of consecutive depression[82].

Category: modifiable by life-style-change, medication and psychotherapy

3.1.1.16. Sleep Disorders and Patterns

Observational and theoretical considerations suggest a link between sleep disorders and vascular event risk[83]: Sleep disorders are highly prevalent in patients at risk for stroke, and obstructive sleep apnea has been linked to increased stroke risk. However, first attempts of CPAP intervention have failed, but need to be interpreted cautiously. Moreover, both short and long sleep as well as insomnia and sleep-related movement disorders have been linked to increased stroke risk. Also, sleep disorders are linked to increases in the prevalence of stroke risk factors[84], which might be at least one pathway through which the increased stroke risk is mediated.

3.1.1.17. Prior stroke/TIA

It is very well established that prior stroke increases the likelihood for further stroke events[85], reaching up to a cumulative risk of 39.2% over a span of 10 years and a considerable variation across studies and locations (5 year risk in Manhattan 19% vs. 32% in Perth)[86].

Category: partially modifiable by life-style-change

3.1.1.18. Neuroimaging findings

In contrast to the primary prevention setting, for secondary prevention neuroimaging findings are available which can be used for secondary stroke risk prediction. Unfortunately, data on the value of these neuroimaging findings for secondary prevention is scarce. A meta-analysis of cerebral microbleeds (CMB) on MR-imaging showed an association between secondary stroke risk and CMBs in western cohorts[87]. Yaghi et al. showed that recurrent stroke can be predicted by presence of stroke and signs of large vessel disease from neuroimaging findings[88].

Category: unmodfiable

3.1.2 Health factors

3.1.2.1. Physical Activity and Exercise

The protective effect of regular physical exercise to lower stroke risk is well established[7,63]. Here, a stronger link between physical exercise and lowered risk for stroke was found than e.g. for mycardial infarction.

3.1.2.2. Healthy diet

Diet can directly influence vascular risk factors. Diets high in saturated fat, trans fat and cholesterol can raise blood cholesterol levels. Diets high in sodium (salt) can increase blood pressure. Diets with high calories can lead to obesity. The INTERSTROKE study[7] established that increased consumption of fruit and fish, but not vegetables, reduced stroke risk, whereas an increased stroke risk was associated with foods like red meat, organ meat, eggs, fried foods, pizza, salty snacks and all foods containing lards. General recommendations for lowering stroke risk include a healthy diet, often the so called "Mediterranean diet" MD is recommended. In 2018, a large cohort study with a 17 year follow up and 395 048 person years found a stroke risk reducing effect, interestingly, however, only for women[89].

3.1.2.3.Medications Compliance

Depending on the prevalence of risk factors medications are given to counter the effects of the underlying conditions. However, the binary assessment whether a patient is medicated or not, is not sufficient to determine the positive effect of the medication, since it is known that compliance - i.e. the adherence to taking the mediation - can differ widely. Xu and colleagues showed recently in a meta-analysis that adherence to anti-hypertensive stroke prevention medication is dose-dependently associated with a lower risk of of stroke in patient at-risk with hypertension[90]. An older study showed that higher age, more severe strokes and cardioembolic stroke causes improved compliance to secondary prevention[91].

3.1.3Resilience factors

Resilience factors determine how well a patient can “bounce back” after a disease event happened. Thus, these factors play a role for the rehab and reintegration phase of stroke, but not for the prevention setting.

3.1.4 Tabular feature and use case view

Feature	Primary Use Case 1	Primary Use Case 2	Primary Use Case 3	Secondary Use Case 1	Secondary Use Case 2	Secondary Use Case 3
Risk Factors						
Age	x		x	x		x
Sex	x		x	x		x
Ethnicity	x		x	x		x
Family history/genetics	x		x	x		x
Hypertension	x		x	x		x
Diabetes	x		x	x		x
Smoking	x		x	x		x
Carotid artery disease	x		x	x		x

Atrial fibrillation	x		x	x		x
Dyslipidemia	x		x	x		x
Obesity	x		x	x		x
Alcohol/substance abuse	x		x	x		x
Vascular disease	x		x	x		x
Stress	x		x	x		x
Depression	x		x	x		x
Sleep disorders	x		x	x		x
prior stroke event				x		x
Neuroimaging				x		x
Health Factors						
Exercise		x	x		x	x
Healthy diet		x	x		x	x
Compliance		x	x		x	x

3.2 Acute Stroke

The following factors relate to patients outcome after stroke. Here the outcome can be defined at discharge in order to not integrate the rehabilitation process as a factor, or as outcome post 3 months, where the rehabilitation process interacts with the other factors. Also, we will define new output targets in the deliverable D4.2 which overcome drawbacks of the currently used.

3.2.1Risk factors

3.2.1.1.Age

Age is known to be one of the most predictive features to measure outcome after stroke or the success of stroke treatment. Many works have established a direct association (e.g.[92–95]. CUB has established their own models for stroke outcome prediction - the results of which will be submitted soon - which confirm these findings.

3.2.1.2.NIHSS

The NIHSS is a clinical score which assesses the severity of ischemic stroke. It has been established - like with age - that NIHSS is one of the most predictive features for outcome after stroke (.e.g.[93–95]). Our model mentioned in 3.2.1.1 confirms these findings.

3.2.1.3.Treatment

Currently two causal treatments exists, the success of which have a direct effect on stroke outcome. Either the relevant blood clot is dissolved using an intravenously applied agent called t-PA or the blood clot is mechanically removed by mechanical thrombectomy. The former- intravenous t-PA - is an established treatment method up to 4.5 hours after stroke[96]. The latter - mechanical thrombectomy showed clinical efficacy in relevant studies in early 2015[97–101]. The studies - MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT - established for the first time a clear and strong clinical benefit for patients, especially those with clearly documented (proximal) vessel occlusions, which were hard to treat with intravenous thrombolysis in the past, were usually more severe strokes (median NIHSS of 17) and had worse outcomes. The profile of this treatment is also convincing with a number-needed-to-treat (NNT) of 1:4 in contrast to intravenous thrombolysis where the NNT is rather in the range of 1:10 for the largest cohort of patients. These changes find reflection in current clinical practice where mechanical thrombectomy has found good adaption, but the process of standardization is still ongoing. Thus, considerable differences in the application of the new treatment can be found across stroke centers.

3.2.1.4.Neuroimaging

Neuroimaging is performed in every patient with stroke, for which it has to be established that the patient suffers from ischemic stroke and not from a brain bleed (hemorrhagic stroke). Here, computed tomography (CT) or - less frequently - magnetic resonance imaging (MRI) is used. In classic predictive approaches of the past, features were (semi-)manually extracted from these images. Here, it was established that stroke lesion volume is associated with stroke outcome (e.g.[102]), which is confirmed by our model mentioned in 3.2.1.1. Other parameters include presence of collaterals[103] or thrombus length[104]. Next to single parameters so called mismatch paradigms were established, which were developed to better select patients for treatment. Amongst them the diffusion-perfusion mismatch, the diffusion-FLAIR mismatch and the clinical-diffusion mismatch. A complete critical evaluation of these paradigms is not the scope of this section. However, it should be mentioned that only one of these - the diffusion-FLAIR mismatch - has shown considerable clinical efficacy in a large recent multicenter trial[10]. However, all these approaches have the drawback that manual feature extraction needs to be performed. Here, modern deep learning architectures have the advantage that the feature extraction process is integrated in the method. A potential application are multi-scale autoencoder architectures, which combine imaging and clinical parameters into one larger network. A large advantage of such architectures is that they can run automatically in the clinical setting.

Another application of neuroimaging is the voxel-wise prediction of post-treatment infarction[105]. These models provide visualization of treatment success.

3.2.1.5. Risk scores

Parsons et al explored the use of the ASPECTS-score and found that a score above 6 points was better in prediction the final outcome than native CT and CT-angiography[106]. The e-ASPECTS score can also be derived automatically and is non-inferior to human radiological assessment[107]. Researchers working on data from the DEFUSE study developed a 5-item scale to predict stroke outcome after middle-cerebral-artery infarction[108]. The 5 independent predictors of stroke outcome were age, NIHSS, infarct volume, admission white cell blood count and presence of hypoglycaemia; combination of these factors in a scale further improved the prediction (AUC: 0.91). Another scores are the DRAGON, SEDAN and ASTRAL scores [109]. For example, in a very large collective of over 4000 patients with both anterior and posterior circulation the DRAGON score achieved an AUC of around 0.83. The THRIVE-c score was validated in a huge database of over 12000 patients and achieved and AUC of 0.74 for the prediction of stroke outcome.

3.2.2 Health factors

In contrast to risk factors, works on health factors for stroke outcome are very scarce.

3.2.2.1. Obesity

Current data suggest the so called "obesity paradoxon" in stroke, although caution is advised as the study data is of low quality[110]. These data show that - while obesity is a risk factor to get stroke - once a stroke occurs obese patients have better stroke outcome.

3.2.3 Resilience factors

Resilience factors determine how well a patient can "bounce back" after a disease event happened. Thus, these factors play a role for the rehab and reintegration phase of stroke, but not for the acute stroke setting.

3.2.4Tabular feature and use case view

Feature	Use Case 1	Use Case 2	Use Case 3	Use Case 4	Use Case 5
Risk Factors					
Age	x	x	x	x	x
NIHSS	x	x	x	x	x
Treatment	x	x	x	x	x
Neuroimaging	x	x	x	x	x
Risk scores	x	x	x	x	x
Health Factors					
Obesity	x	x	x	x	x

3.3 Rehabilitation

3.3.1 Risk factors

3.3.1.1.Neurological medical complications

Although the number of potential medical complications can be extensive for a given patient, we focus on the most common: recurrent stroke, clinical features lasting more than 24 hours consistent with the World Health Organization definition of stroke and epileptic seizure, clinical diagnosis of focal and/or generalized seizure in a previously non-epileptic patient.

3.3.1.2.Spasticity

Spasticity is a common symptom after stroke, arising in about 30% of patients, and usually occurs within the first few days or weeks. However, the onset of spasticity is highly variable and can occur in the short-, medium- or long-term post-stroke period[111].

Risk factors were identified for the development of permanent spasticity after a stroke: (i) any paresis in affected limb, (ii) more severe paresis at 16 weeks compared to the first week, (iii) MAS 2 in at least one joint within 6 weeks after stroke, (iv) more than two joints affected by increased muscle tone, (v) hemispasticity within 6 weeks after stroke and (vi) lower Barthel Index[112].

Several scales have been developed and validated to assess spasticity in patients with brain injury. The two most commonly used are the Modified Ashworth Scale and the Modified Tardieu Scale, both reported in Guttmann databases. These scales assess the degree and angle of muscle contraction and, in the case of retraction, the amplitude of the permitted movement.

3.3.1.3. Aphasia

Approximately one third of patients who survive the acute phase after stroke are aphasic. Aphasia due to stroke is associated with increased mortality, worse functional recovery, and lower chances of returning to work activities.

3.3.1.4. Cognitive impairment

Post-stroke cognitive impairment occurs frequently in the patients with stroke. The prevalence of post-stroke cognitive impairment ranges from 20% to 80%, which varies for the difference between the countries, the races, and the diagnostic criteria affecting several cognitive domains like memory, language, visuoconstruction, executive function, calculation, comprehension and judgme[113].

3.3.1.5. Dementia

Stroke is a major risk factor for the conversion of existing mild cognitive impairment (MCI) to dementia. Risk for developing dementia may be up to 10 times greater among individuals with stroke than for those without.
In a review of studies examining post-stroke dementia, Leys et al. compiled a list of stroke characteristics and features from neuro-imaging studies associated with the development of dementia or cognitive impairment following a stroke even[114]: Severe deficit at onset, Recurrent stroke, Supratentorial lesions, Left hemisphere lesions, Anterior & posterior cerebral artery territory lesions, Strategic infarcts, Multiple lesions.

3.3.1.6. Complications of immobility

Falls: Any documented falls regardless of cause (fall with serious injury defined as one that resulted in fracture, radiological investigation, neurological investigation, or suturing of wound).
Pressure sore/skin break: Any skin break or necrosis resulting from either pressure or trivial trauma (skin trauma directly resulting from falls not included).

3.3.1.7. Thromboembolism

Venous thromboembolism (VTE) is a disorder that includes deep vein thrombosis and pulmonary embolism in both types:
Deep vein thrombosis: Clinical diagnosis of deep vein thrombosis
Pulmonary embolism: Clinical diagnosis of pulmonary embolism

3.3.1.8. Chronic Pain

Around 30% of stroke survivors experience pain. Pain after stroke can be nociceptive or neuropathic. Nociceptive pain nociceptive pain is the most common type. It’s caused by potentially harmful stimuli being detected by nociceptors around the body. Neuropathic pain is pain caused by damage or disease affecting the somatosensory nervous system. Neuropathic pain may be associated with abnormal sensations called dysesthesia or pain from normally non-painful stimuli (allodynia). It may have continuous and/or episodic (paroxysmal) components. The latter resemble stabbings or electric shocks. Common qualities include burning or coldness, "pins and needles" sensations, numbness and itching.

3.3.1.9. Bladder and Bowel Dysfunction

Around half of stroke patients will suffer from some form of incontinence, for many this is temporary whilst the brain injury heals. Stroke patients can suffer from both bladder and bowel incontinence. Below are some of the reasons why incontinence happens

Urinary Incontinence: urge urinary incontinence (UUI), stress urinary incontinence (SUI), and mixed urged and stress urinary incontinence.

Urinary retention: Acute urinary retention due to inactivity or hyporeflexia of the detrusor muscle

3.3.2 Health factors

3.3.2.1. Cognitive training (non-aphasic)

Computerized tasks are increasingly being applied over traditional paper and pencil activities. In this work the Guttmann, NeuroPersonalTrainer ® platform (https://www.gnpt.es/en) *GNPT*, is the cognitive rehabilitation framework applied for treatment systematization[115]. While task repetition is not the only important feature, it is becoming clear that neuroplastic change and functional improvement occur after specific tasks are performed, but do not occur with others[116]. Thus, one important focus for rehabilitation professionals is the treatment configuration, described for example in terms of number of rehabilitation sessions, number of tasks executions and different tasks performed during treatment.

In Clinical Pharmacokinetics, therapeutic range is defined as a range of drug concentrations within which the probability of the desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low. Within this therapeutic range the desired effects of the drug are observed. Below it there is a greater probability that the therapeutic benefits are not realized (non-response or treatment-resistance); above it, toxic effects may occur. Using this analogy, we consider that a cognitive rehabilitation treatment task behaves in **NRR** if the desired clinical response is obtained i.e. if an observable improvement in the targeted cognitive function is registered for the patient.

Use Case 3 and Use Case 5 defined in Section 1.3.3 and 1.3.5 aim to extend our previous work in NRR[115] to non-aphasic treatments.

3.3.2.2. Cognitive training (aphasic)

Use Case 3 and Use Case 4 defined in Section 1.3.4 and 1.3.6. for aphasic patients respectively, aim to extend our previous work in predictive models[117] where we statistically compared 48 predictive techniques (with extensive parameters tuning), from 12 predictive models considering 3 different resampling methods. We applied model-dependent and model-independent ranking techniques to assess variables' importance. We selected techniques from linear modeling; such as Partial Least Square or Generalized Linear Model to Neural Network models as an important class of non-linear predictive models. From kernel methods, we selected Support Vector Machine with a Gaussian kernel as it is capable of dealing with non-linearity and data noise. Random Forests and Boosted trees are considered in this analysis since they are well-known ensemble-based techniques. We also included partition and rule based methods as well as a basic prediction technique, i.e. k-Nearest Neighbors.

3.3.2.3. Upper limb training

Standard upper limb rehabilitation after stroke typically includes neurofacilitation techniques, task-specific training and task-oriented training. Further approaches include strength training, trunk restraint, somatosensory training, constraint-induced movement therapy, bilateral arm training, coordination of reach to grasp, mirror training, action observation and neuromuscular electrical stimulation

3.3.2.4. Lower limb training

Gait training can take a number of forms, but repetition of the actual motions performed during walking is the most important factor. Parallel bars may be used to help with gait training, especially in the early stages when a patient is first learning or re-learning to walk. They involve a person walking between two handrails to support themselves, often with the therapist either helping to support the patient or physically moving the patient's legs. Gait trainer or other gait aids are also utilized.

Use Case 1 and Use Case 2 defined in Section 1.3.1 and 1.3.2 address physical interventions and take as starting point Task 1.1. presented in D1.1 where we address systematic review on rehabilitation interventions and outcomes[118] where we identified 21 physical rehabilitation interventions e.g.. transcranial Direct Current Stimulation, repetitive Transcranial Magnetic Stimulation, repetitive Peripheral Magnetic Stimulation, Repetitive Task Training, Robotic gait training upper limb, robotic gait training lower limb, Hydrotherapy and Virtual Reality several of them performed at Institut Guttmann.

3.3.2.5. Psychological support

Psychological care for this group is as essential as physical rehabilitation, particularly as people with stroke and their families endeavour to manage the impact of stroke on their lives in the short and long term. Guidance is given for establishing pathways and processes to assess and manage the psychological impact of stroke for both emotional and cognitive disorders.

3.3.3 Resilience factors

Standardized assessment scales administered to patients (and also relatives or informal caregivers and clinicians when adequate) in rehabilitation phase addressing several resilience factors presented in Section 2.5 are reported in Institut Guttmann databases.

For example in relation to Individual disposition introduced in Section 2.5.1 several items of HIBS scale[119] evaluate e.g. Difficulty in becoming interested in things (Item 12), Lack of initiative, does not think for him/herself (Item 13); Depressed, low mood (Item 17); Lacks motivation, lack of interest in doing things (Item 20).

Other important aspects are reported also in HIBS scale, for example regarding Intrapersonal factors introduced in Section 2.5.6 (Frequent complaining (Item 3), Argumentative; often disputes topics (Item 6), Lacks control over behaviour; behaviour is inappropriate for social situations (item 7). Irritable; snappy; grumpy (Item 14).

Another scale assessing factors presented in Section 2.5 is the Patient Competency Rating Scale (PCRS), Section 2.5.2 introduces Competency, a specific PCRS subsection addresses Meeting responsibilities and also for example regarding Section 2.5.3 Self-esteem it is addressed in PCRS Emotional subscale.

Section 2.5.4 refers to Social support, which is addressed in several items of Community Integration Scale (CIQ) in the Activities Associated with Socialization subscale e.g. Approximately how many times a month do you usually visit your friends or relatives? (item 8) or Do you have a best friend with whom you confide? (item 12).

Interpersonal factors introduced in section 2.5.6 are also addressed by several items in the Social and Family Appraisal Scale, reported also in Guttmann databases, which is based in the Gijon scale (García-Gonzalez et al 1993) . Social support factor (Section 2.5.4) is addressed also by means of the Social Scale of the Institut Guttmann (ESIG, 7 items) (details are presented in Gibert et al [120].

3.3.4 Tabular feature and use case view

Feature	Rehab Use Case 1	Rehab Use Case 2	Rehab Use Case 3	Rehab Use Case 4	Rehab Use Case 5	Rehab Use Case 6
Risk Factors						
Neurological complications	x					
Spasticity		x				
Dementia			x		x	
Aphasia				x		x
Immobility	x					
Thromboembolism	x					
Chronic Pain	x					
Cognitive impairment			x		x	
Bladder and Bowel	x					
Health Factors						
Cognitive training (non-aphasic)			x		x	
Cognitive training (aphasic)				x		x
Upper limb training	x	x				

Lower limb training	x					
Psychological support	x					
Resilience Factors						
Individual disposition	x		x	x	x	x
Competency			x	x	x	x
Social support	x	x	x	x	x	x
Emotional support	x	x	x	x	x	x
Intrapersonal factors: Motivation			x	x	x	x
Intrapersonal factors: Perseverance	x	x	x	x	x	x

3.4 Reintegration

3.4.1 Risk factors

3.4.1.1. Depression

Depression is a common complication of stroke. Prevalence of depression (major and minor) has been reported to affect 23-40% of stroke patients. Depression post stroke is associated with: Increased physical impairment and decreased physical recovery, increased cognitive impairment, decrease social participation and quality of life, increased risk for mortality, Increased risk of depression for informal caregivers, increase healthcare utilization for both.

3.4.1.2. Apathy

Apathy can occur as an independent syndrome, although it may also occur as a symptom of depression or dementia Patients present with loss of motivation, concern, interest, and emotional response, resulting in a loss of initiative, decreased interaction with their environment, and a reduced interest in social life.

3.4.1.3. Lack of social support

Social environments that foster a sense of support and belonging allow stroke patients to increase their motivation of participating in group activities. Important sources of social support are family members and close friends which can provide substantial practical and emotional support.

3.4.1.4. Lack of accessibility

Patients have reported environmental barriers from unsafe sidewalks to a lack of accessible entrances that prevent them from even leaving their homes, as well as lack of accessibility and limited access to various public/community centres due to environmental constraints.

3.4.1.5. Loss of functional independence in ADLs

include the fundamental skills typically needed to manage basic physical needs, comprised the following areas: grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating, and eating.

3.4.1.6. Lack of information (caregivers)

Family or informal caregivers often feel unprepared for the role, informal caregivers may find themselves in the position of having to provide skilled nursing assistance to the stroke survivor while having little or no experience in delivering appropriate care and support. They often receive no training or instruction and, therefore, have no choice but to learn what is required of them in their new role by trial and error.

3.4.1.7. Lack of information (stroke survivor)

Although the provision of information and education is an important need identified by stroke patients and their informal caregivers, it is often unfulfilled. Community dwelling stroke survivors most often identify information needs in the areas of recurrence and secondary prevention, patient safety, cognitive and emotional problems, specific and individual consequences of stroke, medication management, communication difficulties, and access to further information, community resources and stroke support groups.

3.4.2 Health factors

3.4.2.1. Periodic Integral Visit

All patients receiving care at the Institut Guttmann are followed-up after their clinical discharge. All of them are periodically reassessed every 12–18 months by the Periodic Integral Visit (PIV).

PIEs are conducted to support them to achieve their best level of personal autonomy as possible, as well as promote their QoL and their social reintegration. It is also aimed to permit early detection of some pathologies which, because of a baseline neurological lesion, might be asymptomatic till more advanced phases. Early detection can decrease medical complications, preventing long hospitalization, or even survival risks.

Medical, functional, psycho/neuropsychological and social aspects as well as health-education and health risk prevention are evaluated in the PIE with a total of 147 items. Institut Guttmann currently measures QoL by using several assessment scales, all included in the PIE, according to multidimensional and multi-disciplinary models.

3.4.2.2. Psychological support

Psychological care for this group is as essential as physical rehabilitation, particularly as people with stroke and their families endeavour to manage the impact of stroke on their lives in the long term. Guidance is given for establishing pathways and processes to assess and manage the psychological impact of stroke for both emotional and cognitive disorders.

Use Case 3 presented in Section 1.4.3 aim to extend our previous research(Gibert et al. 2009), where we identified QoL trajectories, within a subset of 32 items from the PIE dataset in the following QoL domains: a) Emotional wellness, measured through the instrument IBP (6 subscales); b) Functional Autonomy: Using the scores on the corresponding 19 items of the ICF, Disability and Health; including ADLs, transfer, cognitive and social activities; c) Social Inclusion by means of the Social Scale of the Institut Guttmann (ESIG, 7 items).

Use Case 1, 2 and 4 presented in Sections 1.4.1, 1.4.2 and 1.4.4 extend our previous work (Subirtats et al 2013) in relation to QVidLab (QoL Laboratory) platform aiming for: (1) providing stroke survivors, their relatives, health professionals, therapists, carers and institutions with an interoperable platform that supports standard indicators, (2) promoting knowledge democratization and user empowerment, and (3) allowing making decisions with a more informed opinion.

3.4.3 Resilience factors

Standardized assessment scales administered to patients (and also relatives or informal caregivers and clinicians when adequate) in reintegration phase addressing several resilience factors presented in Section 2.5 are reported in Institut Guttmann databases.

For example in relation to Individual disposition introduced in Section 2.5.1 several items of HIBS scale (Hamish et al 2003) evaluate e.g. Difficulty in becoming interested in things (Item 12), Lack of initiative, does not think for him/herself (Item 13); Depressed, low mood (Item 17); Lacks motivation, lack of interest in doing things (Item 20). Other important aspects are reported also in HIBS scale, for example regarding Intrapersonal factors introduced in Section 2.5.6 (Frequent complaining (Item 3), Argumentative; often disputes topics (Item 6), Lacks control over behaviour; behaviour is inappropriate for social situations (item 7). Irritable; snappy; grumpy.(Item 14)

Another scale assessing factors presented in Section 2.5 is the Patient Competency Rating Scale (PCRS), Section 2.5.2 introduces Competency, a specific PCRS subsection addresses Meeting responsibilities and also for example regarding Section 2.5.3 Self-esteem it is addressed in PCRS Emotional subscale.

Section 2.5.4 refers to Social support, which is addressed in several items of Community Integration Scale (CIQ) in the Activities Associated with Socialization subscale e.g. Approximately how many times a month do you usually visit your friends or relatives? (item 8) or Do you have a best friend with whom you confide? (item 12).

Interpersonal factors introduced in section 2.5.6 are also addressed by several items in the Social and Family Appraisal Scale, reported also in Guttmann databases, which is based on the Gijon scale[121]. Social support factor (Section 2.5.4) is addressed also by means of the Social Scale of the Institut Guttmann (ESIG, 7 items) (details are presented in Gibert et al[120].

3.4.4 Tabular feature and use case view

Feature	**Reintegration Use Case 1**	**Reintegration Use Case 2**	**Reintegration Use Case 3**	**Reintegration Use Case 4**
Risk Factors				
Depression		x	x	x
Apathy	x	x	x	x
Lack of social support		x	x	
Lack of accessibility		x		
Loss of functional independence	x	x	x	x
Lack of information (caregiver)			x	x
Lack of information (stroke survivor)		x	x	x
Health Factors				
Periodic Integral Visit	x	x	x	x
Psychological support	x	x	x	x
Resilience Factors				
Individual disposition	x	x	x	x
Competency	x	x	x	x
Social support	x	x	x	x
Emotional support	x	x	x	x

Intrapersonal factors: Motivation	x	x	x	x
Intrapersonal factors: Perseverance	x	x	x	x

4 Conclusions

In this deliverable we have provided the updated list of use cases for each phase of stroke, have outlined our definitions of risk-, health- and resilience-factors and also summarized an extensive feature overview with feature - use case matrices. This will - together with D4.2. - facilitate the modelling endeavours within P4Q by providing a common ground for discussion, model building and study planning.

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