PRECISE4Q

PREDICTIVE MODELLING IN STROKE

DELIVERABLE

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D5.4 – Study design rehabilitation/reintegration

Revision History, Status, Abstract, Keywords, Statement of Originality

Revision History

Revision	Date	Author	Organisation	Description
V1	12/04/2019	Alejandro García, Joan Saurí, Eloy Opisso	GUT	General protocol description and draft of the proposed studies
V2	26/04/2019	Alejandro García, Joan Saurí, Eloy Opisso	GUT	Second version of the proposed studies and tailoring of the general protocol to each of them
V3	29/04/2019	Alejandro García, Joan Saurí, Eloy Opisso	GUT	Final version

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Abstract (for dissemination)	This deliverable describes the activities to be conducted in order to achieve objective 2 of WP5 (Clinical Studies for Model Validation). Objective 2 aims to design and conduct a clinical validation study for rehabilitation/reintegration phases, this document addresses the study design, described in T5.4 during M1-M12 period. The clinical validation will be executed as described in T5.5 (M13-M36 period) and will be reported in D5.5. deliverable. This document presents three main sections: first a general description of the clinical study protocol and then the tailoring of the protocol to 1) the rehab phase and 2) the follow up phase. The main questions to be addressed within the validation studies are described in deliverable D4.1 (White paper on stroke risk, health and resilience factors). Specifically, we propose 3 studies (studies #1 and #2 for rehabilitation phase and study #3 for reintegration phase): 1- Cognitive training using Gutmann NeuroPersonal Trainer database with the intervention obtained from predictive models that will provide new Neuro Rehabilitation Ranges and optimal number of sessions, tasks, treatment durations (as well as other relevant parameters described in D4.1). .2- Functional upper limb training involving physical therapy with the intervention obtained from predictive models that will provide us optimal treatment durations, optimal number of sessions of occupational therapies, movement therapies or AVDs activities. 3- Community integration based on psychosocial risk model, intervention here is performed during rehabilitation phase (early interventions addressed during rehabilitation phase are expected to produce an impact in reintegration phase). It will be based in the risk trajectories that will be identified by the predictive models involving main community integration

	assessments
Keywords	Validation, rehabilitation, reintegration, arm, cognitive, trajectories

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.

Table of Content

Executive Summary

This deliverable describes the activities to be conducted in order to achieve objective 2 of WP5 (Clinical Studies for Model Validation).

Objective 2 aims to design and conduct a clinical validation study for rehabilitation/reintegration phases, this document addresses the study design, described in T5.4 during M1-M12 period. The clinical validation will be executed as described in T5.5 (M13-M36 period) and will be reported in D5.5. deliverable.

This document presents three main sections: first a general description of the clinical study protocol and then the tailoring of the protocol to 1) the rehab phase and 2) the follow up phase. The main questions to be addressed within the validation studies are described in deliverable D4.1 (White paper on stroke risk, health and resilience factors).

Therefore, clinical validation studies described in this document take as starting point the use cases defined in deliverable D4.1 for rehabilitation and follow up phases. Specifically, we propose 3 studies (studies #1 and #2 for rehabilitation phase and study #3 for reintegration phase):

1- Cognitive training using Gutmann NeuroPersonal Trainer database with the intervention obtained from predictive models that will provide new Neuro Rehabilitation Ranges and optimal number of sessions, tasks, treatment durations (as well as other relevant parameters described in D4.1).

.2- Functional upper limb training involving physical therapy with the intervention obtained from predictive models that will provide us optimal treatment durations, optimal number of sessions of occupational therapies, movement therapies or AVDs activities.

3- Community integration based on psychosocial risk model, intervention here is performed during rehabilitation phase (early interventions addressed during rehabilitation phase are expected to produce an impact in reintegration phase). It will be based in the risk trajectories that will be identified by the predictive models involving main community integration assessments.

1 Scope and Purpose

This deliverable describes the activities to be conducted in order to achieve objective 2 of WP5 (Clinical Studies for Model Validation).

Objective 2 aims to design and conduct a clinical validation study for rehabilitation/reintegration phases, this document addresses the study design, described in T5.4 during M1-M12 period. The clinical validation will be executed as described in T5.5 (M13-M36 period) and will be reported in D5.5. deliverable.

This document presents three main sections: first a general description of the clinical study protocol and then the tailoring of the protocol to 1) the rehab phase and 2) the follow up phase.

The main questions to be addressed within the validation studies are described in deliverable D4.1 (White paper on stroke risk, health and resilience factors).

Therefore, clinical validation studies described in this document take as starting point the use cases defined in deliverable D4.1 rehab and follow up phases, use cases are briefly described before presenting the specific activities of the general protocol for both phases.

2 Validation studies: General protocol

Validation studies regarding rehabilitation and reintegration phases will be conducted by GUT, four studies are planned: two addressing rehabilitation phase and two addressing reintegration phase.

The number of patients participating in rehabilitation phase by year (at the moment of submission of this deliverable) are presented in Table 1. The first validation study (presented in Chapter 3 of this deliverable) will address cognitive training in Guttmann NeuroPersonal Trainer platform (GNPT). Therefore Table 1 presents total ischemic stroke patients following GNPT. The second validation study (presented in Chapter 4 of this deliverable) will address functional rehabilitation, therefore Table 1 also presents number of patients not following GNPT, those patients will be mainly involved in Chapter 4 validation study.

Every stroke patient, after discharge from GUT 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. 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.

Therefore, the number of patients involved in the reintegration phase study (presented in Chapter 5) will be similar to those presented in Table 1.

Year	GNPT	NO GNPT	Total
2007	4	33	37
2008	6	76	82
2009	6	79	85
2010	16	85	101
2011	31	71	102
2012	39	51	90
2013	52	73	125
2014	54	79	133
2015	73	59	132
2016	77	61	138
2017	66	72	138
2018	70	79	149
2019	25	33	58
	519	**851**	**1370**

Table 1. Number of patients in rehabilitation phase (performing GNPT and not)

This chapter presents the general protocol to be applied in each validation study. The contents of the validation studies presented in the upcoming chapters will follow the general structure presented in the following subsections of Chapter 2. Studies will then tailor this general protocol to the specific characteristics required for each of them.

2.1 General information

It may be useful to include a brief synopsis of the study for quick reference and/or to use as a standalone document. Complete information and, if required, add additional rows.

Study Title	Please ensure this is in accordance with the title page and the IRAS form		
Clinical Phase	Rehabilitation/Reintegration		
Design	Prospective/Observational/Interventional…		
Participants	General description		
Sample Size	Include the total number of participants of the study for both intervention phase and for collecting relevant dataset for building predictive models		
Planned Period	Include the planned period of the study for both intervention phase and for collecting relevant dataset for building predictive models		
Planned Recruitment period	Indicate start and end dates for recruitment for intervention phase		
	Objectives	Outcome Measures	Timepoint(s)
Primary			
Secondary			

2.2 Background and rationale

Summarise briefly the main characteristics of the problem being studied and any possible opportunity for better treatment. Include information on the current standard activities with indication as to why a trial of a new intervention is needed. Description of the population to be studied. References to related literature that is relevant to the study and that provide background for the study.

2.3 Objectives and outcomes measures

There is usually only one primary objective, the rest are secondary objectives. The wording of the objectives and outcomes provided below should be clear, unambiguous and as specific as possible – the trial will be judged on how, and how well, the objectives were satisfied. The definitions should include specific measurement variables (e.g., systolic blood pressure or Incidence and severity of adverse events or Disability Rating Index etc.,) analysis metrics (e.g., change from baseline measurement or time to event etc.,) and, where relevant, the time point for each outcome measure. Additional more detailed descriptions and definitions of outcomes for all primary and secondary outcomes may also be provided elsewhere in the protocol (e.g., in the statistics section) with a cross reference to the summary information here.
Complete table below with all relevant information.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective	Describe the outcome measures and how/when they will be measured during the study. Outcome measures should reflect the objectives. It is important that only one primary outcome measure is selected as it will be used to decide the overall results or 'success' of the study. The primary outcome measure should be measurable, clinically relevant to participants and widely accepted by the scientific and medical community.	
Secondary Objectives	As above	
Exploratory Objectives	As Above	

2.4 Study design

Briefly summarise the overall trial design by type of trial (e.g., retrospective, prospective, observational,…).

Briefly summarise the study setting (e.g., hospitals, GP surgeries, care homes, academic centres etc.) indicating number of trial sites, types of site (e.g., recruiting, providing intervention, continuing care etc.,).

Give the expected duration of participant involvement providing concise details of the number of visits, including description of the sequence and duration of all study phases, if appropriate.

Briefly describe processes for collecting data, and why this method will be used (e.g. type of equipment, questionnaire, interview schedule, observation schedule).

Include a flowchart for the study as a whole (here, or as an appendix), if appropriate.

2.5 Participants description

In this section we describe the main characteristics of participants, inclusion and exclusion criteria (amend as appropriate)

2.5.1 Study participants

Give an overall description of the study participants.

2.5.2 Inclusion criteria

Give an overall description of the inclusion criteria, for example:
Example criteria only (amend as appropriate): Participant is willing and able to give informed consent for participation in the study, Male or Female, aged 18 years or above.

2.5.3 Exclusion criteria

Give an overall description of the inclusion criteria, for example:
The participant may not enter the study if ANY of the following apply: Significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anaesthesia during the study period.

2.6 Study procedures

In this section we describe the main procedures involved in the study (amend as appropriate)

2.6.1 Recruitment

Describe how potential participants will be identified, approached and recruited (follow up phase requires specific procedures). .

2.6.2 Regulatory clearance

In this section we address the informed consent, ethics and data protection e.g. specify who will take Informed Consent, how, and when it will be taken. Informed Consent must be obtained prior to any study related procedures being undertaken.

2.6.3 Baseline assessments

Specify and describe all baseline assessments. They must reflect the objectives and outcome measures.

2.6.4 Data management

If not detailed previously, describe the data that will be studied from each participant (e.g. age, educational level, rehabilitation sessions, tasks, obtained results in tasks executions, etc.).
Clarify in this section whether the data referred to in the study is taken as part of a standard rehabilitation treatment with the results accessed by the research team or are research specific data for analysis under this study.

2.6.5 Withdrawal of participants

During the course of the study a participant may withdraw early from it at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary. Provide justification for any procedures and observations that will be required following a complete withdrawal.
Ensure that the appropriate information on these arrangements is included in the participant Informed Consent.

2.6.6 Definition of the end of the study

The definition of end of study must be provided. Where long term follow up of participants is planned, the end of study must include that follow-up period.

2.7 Study Interventions

Describe the specific interventions being validated in the study. If there is an additional investigational intervention such as radiotherapy, surgery or device use provide the relevant details here. If there are no additional interventions in the study design, please state that clearly.

2.8 Statistical analysis

In this section we describe the main procedures involved in the statistical analysis of the study (amend as appropriate).

2.8.1 Description of statistical methods

Describe the statistical methods to be employed for analysing primary and secondary outcomes. If not provided elsewhere detailed descriptions and definitions of outcomes for all primary and secondary outcomes should be provided here including specific measurement variables, analysis metrics and, where relevant, the time point for each outcome measure. If already described elsewhere, provide cross reference to the relevant protocol section.

2.8.2 Sample size determination

Justify choice of sample size, i.e., how was it determined including reflections on (or calculations of) the power of the trial, any statistical assumptions or clinical justifications (where for e.g., the sample size was not arrived at statistically, due to rarity of the disease etc.).
Take into account any potential withdrawals.

2.9 Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the Ethical regulations.

3 Rehabilitation phase: Clinical study #1 – Cognitive training

As described in D4.1 computerized cognitive training is increasingly replacing traditional "paper and pencil" activities, therefore this study focuses on supporting clinicians in the decisions related to the elaboration of therapeutic plans addressing computerized cognitive rehabilitation contents in GNPT platform.

3.1 General information

Study Title	Cognitive training in GNPT platform		
Clinical Phase	Rehabilitation		
Design	Interventional		
Participants	Ischemic stroke patients with cognitive impairments in main functions involved in ADLs (attention, memory, executive functioning)		
Sample Size	600 for building predictive models 100 for interventional study		
Planned Period	2007-2019 for collecting dataset for building predictive models M13-M24 for building predictive models using the collected dataset M24-M36 (April 2020- April 2021) for interventional study		
Planned Recruitment period	M2 4-M36 (April 2020-April 2021)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Improvement in cognitive functions involved in main ADLs activities	Standard cognitive assessment scales (as described in deliverable D1.3 section 5.1.1).	End of rehab phase
Secondary	Reduction of level of non-compliance along treatment	Number of tasks in NRR (NRR as described in D1.3 section 5.1.3)	End of rehab phase

3.2 Background and rationale

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.
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.

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.
In GNPT, following the execution of a given task T the subject gets a result RT ranging from 0 to 100. A 0 result denotes the lowest level of task completion and a 100 the highest. Being the NRR of task T defined as NRR(T) = [r-, r+], and being r-, r+ in [0, 100], using a simple test it is easy to determine whether or not the patient performed the task in NRR (García-Rudolph and Gibert, 2016) :NRR (RT) iff $RT \in NRR(T) \equiv r- \leq RT \leq r+$ Currently, some hypotheses are being tested for the values of r- and r+. For example nowadays we consider that *r- = 65* and *r+= 85 i.e. NRR(T) =[65,85].*

3.3 Objectives and outcomes measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation**
Primary Objective Obtain deficit reductions in cognitive functions regarding global cognitive response (pre-post treatment global difference) and regarding individual functions responses (pre-post treatment function difference). Treatment selection of tasks are based on NRR identified by predictive models	Standard cognitive assessment scales (as described in deliverable D1.3 section 5.1.1) e.g. Wechsler Adult Intelligence Scale (WAIS-III), Trail Making Test (Part A and Part B), The Stroop Color and Word Test (SCWT), Wisconsin Card Sorting Test (WCST), Continuous Performance Task Test (CPT), Letter Fluency Test, TB Orientation test, Overlapping Images (Wechsler),The Rey Auditory Verbal Learning Test (RAVL)	End of rehabilitation treatment (treatments take between 2-5 months)
Secondary Objectives Reduction of level of non-compliance along treatment. Level of compliance at a global level (considering every function) or level of compliance at the function level (e.g. compliance when considering only attention or memory functions)	Measures of compliance are considered at the level of tasks, session or treatment. NRR is used as measure of compliance (tasks performed at NRR are considered as completed)	End of rehabilitation treatment (treatments take between 2-5 months)

3.4 Study design

The overall study design is interventional, training dataset for building predictive models are obtained from previous GNPT rehabilitation treatments (number of patients are presented in Table 1).

The study setting is the Neuropsychology unit of Institut Guttmann, Neurorehabilitation Hospital.

Participant involvement will be the same as in usual cognitive training, 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.

3.5 Participants description

Participants are following standard rehabilitation treatment after ischemic stroke at Institut Guttmann.

3.5.1 Study participants

Ischemic stroke patients with cognitive impairments in main functions involved in ADLs (attention, memory, executive functioning undertaking cognitive rehabilitation treatment in GUT by means of GNPT platform.

3.5.2 Inclusion criteria

Participant is willing and able to give informed consent for participation in the study, if not able to give informed consent it will be provided by a representative. Male or Female, aged 18 years or above. Treatment aimed at all those patients partially oriented, out of Post Traumatic Amnesia (APT) whose attention, motor and sensitivity ability allows them to perform cognitive treatment with computer support.
The Guttmann NeuroPersonal Trainer (GNPT) platform is used to perform computerized cognitive treatment, enabling personalized and individualized rehabilitation based on the cognitive profile of the patient defined by the initial neuropsychological evaluation.

3.5.3 Exclusion criteria

Patients not partially oriented, still in Post Traumatic Amnesia (PTA) or patients whose attention, motor and sensitivity ability do not allow them to operate a personal computer or laptop.

3.6 Study procedures

The main procedures involved in the study are integrated to standard care in rehabilitation treatments at GUT.

3.6.1 Recruitment

Participants will be identified by their internal (anonymized) GNPT idPatient, interventions addressed in this study as part of standard cognitive treatment will be supported by the PRECISE4Q predictive models therefore patients recruitment will be as in usual treatment.

3.6.2 Regulatory clearance

Clinical studies at GUT require an initial approval by Research and Innovation Committee (RIC) where the study protocol is presented and evaluated, after acceptance RIC decides if the study requires Ethical Committee approval (EC).
EC reviews the study protocol, the Study Informative Sheet (SIS), the Informed Consent (IC) and the Informed Questionnaire (IQ) of the study.
The Study Informative Sheet explains the study to the participants, the expected effects, possible complications (if exist) , what the study implies to the patient.

In the Informed Questionnaire of the study several questions are asked to the participant to assess if he/she understood the informed Consent and its implications.
In case of legal incapacity, a representative or tutor of the patient will sign SIS, IC and IQ.

3.6.3 Baseline assessments

Baseline assessments involve standard cognitive assessment scales (as described in deliverable D1.3 section 5.1.1) e.g. Wechsler Adult Intelligence Scale (WAIS-III), Trail Making Test (Part A and Part B), The Stroop Color and Word Test (SCWT), Wisconsin Card Sorting Test (WCST), Continuous Performance Task Test (CPT), Letter Fluency Test, TB Orientation test, Overlapping Images (Wechsler), the Rey Auditory Verbal Learning Test (RAVL).

3.6.4 Data management

The data referred to in this study is taken as part of the standard rehabilitation treatment with the results accessed by the research team.

3.6.5 Withdrawal of participants

During the course of the study a participant may withdraw early from it at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary. Provide justification for any procedures and observations that will be required following a complete withdrawal.
Ensure that the appropriate information on these arrangements is included in the participant Informed Consent.

3.6.6 Definition of the end of the study

As described in T5.5 end of study is planned for M36 (April 2021)

3.7 Study Intervention

Primary objective of the intervention is to obtain deficit reductions in cognitive functions regarding global cognitive response (pre-post treatment global difference) and regarding individual functions responses (pre-post treatment function difference). The intervention is based in the treatment selection of tasks obtained from NRR identified by predictive models generated during M13-M24 period and performed during the M24-M36 period (April 2020- April 2021).
Secondary objective of the intervention is to Reduce levels of non-compliance along treatment. Reductions are aimed at level of compliance considering a global level (every function) or level of compliance at the function level (e.g. compliance when considering only attention or memory functions). The intervention is based in the treatment selection of tasks obtained from predictive models generated during M13-M24 period and performed during the M24-M36 period (April 2020-April 2021).

3.8 Statistical analysis

Statistical comparisons involving intervention group and previous cognitive rehabilitation treatments (patients presented in Table 1 of this document).

3.8.1 Description of statistical methods

Pre-post statistical comparisons involving demographic variables (e.g. age, gender, level of education, time since injury), treatment data (e.g. number of GNPT sessions, duration of treatment, number of GNPT tasks per session, total number of performed GNPT tasks, total number of GNPT tasks in NRR) and standard cognitive assessment scales (as described in deliverable D1.3 section 5.1.1) e.g. Wechsler Adult Intelligence Scale (WAIS-III), Trail Making Test (Part A and Part B), The Stroop Color and Word Test (SCWT), Wisconsin Card Sorting Test (WCST), Continuous Performance Task Test (CPT), Letter Fluency Test, TB Orientation test, Overlapping Images (Wechsler), the Rey Auditory Verbal Learning Test (RAVL).

3.9 Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the Ethical regulations, following clearance described in section 3.6.2

4 Rehabilitation phase: Clinical study #2 – Motor rehabilitation – arm and hand functioning

Upper limb (i.e.arm, hand and/or finger) motor impairments are often persistent and disabling (Lai 2002); only 20% to 56% of all stroke survivors regain useful upper limb function after three months (Pollock et al 2013). Upper limb motor functions are strongly related to performance in activities of daily living (ADL) (Sveen 1999), particularly in personal activities such as feeding, dressing and grooming. One year after stroke, arm motor impairment is associated with a poorer perception of health-related quality of life and subjective well-being (Franceschini 2010). Therefore, improving upper limb function is a core element of rehabilitation after stroke in order to maximise patient outcomes and reduce disability (Langhorne2003).

4.1 General information

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Study Title	Motor rehabilitation arm and hand functioning		
Clinical Phase	Rehabilitation		
Design	Interventional		
Participants	Ischemic stroke patients with motor impairment in hand and arm function		
Sample Size	600 for building predictive models 100 for interventional study		
Planned Period	2007-2019 for collecting dataset for building predictive models M13-M24 for building predictive models using the collected dataset M24-M36 (April 2020- April 2021) for interventional study		
Planned Recruitment period	M2 4-M36 (April 2020-April 2021)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Improvement in upper limb motor functions involved in main ADLs activities	Standard assessment scales evaluating upper limb functioning e.g. The National Institutes of Health Stroke Scale (NIHSS), the Functional Independence Measure (FIM) (Upper body dressing)	End of rehab phase
Secondary	Reduction in behaviour and distress scores	Head Injury Behaviour Scale (HIBS)	End of rehab phase

4.2 Background and rationale

Professionals responsible for the delivery of upper limb rehabilitation interventions most commonly include physical therapists and occupational therapists. However, other professionals (e.g.nurses, doctors) and non-health professionals (e.g. exercise professionals, carers, family members) may also contribute to delivery of interventions (Coupar 2012). Generally, the interventions used by rehabilitation professionals will consider each patient's goals and be selected after an assessment of a patient's upper limb impairments, together with their effects on activity and participation (Langhorne 2011). However, upper limb rehabilitation interventions could also be delivered as part of a group exercise class or circuit-training. There is a wide range of interventions that can be delivered in an attempt to improve the function of the upper limb after stroke. Such interventions may be aimed at particular impairments (e.g. muscle weakness) or functional abilities (e.g. grasp and release). Clinically, however, the multifactorial deficits and secondary complications require a complex intervention that integrates a number of techniques to address these problems. Some of the most relevant interventions are: (1) 'Hands-on' therapies: the arm and hand joints may be moved by a therapist, using partial or full assistance if the patient's active control is inadequate: such movement may be aimed at maintaining joint and tissue mobility. (2) Exercises and functional movement-based interventions: Exercises can be used for upper limb rehabilitation in a variety of ways. Muscle strength training is directed at working a specific muscle, or group of muscles, using voluntary control. Movement may be assisted or resisted by a therapist or gym equipment. Alternatively, exercises may be done in classes directed by a therapist, utilise a number of exercise machines, or involve circuit training. Task-specific training, also referred to as functional training or ADL training involves practice of tasks relevant to daily life, including part and whole task practice. Repetitive task training involves the repeated practice of functional tasks (generally whole task practice).

4.3 Objectives and outcomes measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation**
Primary Objective Obtain deficit reductions in arm and hand motor functioning	Standard motor assessment scales The National Institutes of Health Stroke Scale (NIHSS), the Functional Independence Measure (FIM) (Upper body dressing)	End of rehabilitation treatment (treatments take between 2-5 months)
Secondary Objectives Reduce behavioural disorders outcomes	Head Injury Behaviour rating scale (HIBS)	End of rehabilitation treatment (treatments take between 2-5 months)

4.4 Study design

The overall study design is interventional, training dataset for building predictive models are obtained from previous rehabilitation (number of patients shown in Table 1).

The study setting is the Functional rehabilitation unit of Institut Guttmann, Neurorehabilitation Hospital.

Participant involvement will be the same as in usual functional training, a standard upper limb rehabilitation treatment.

4.5 Participants description

Participants are following standard motor rehabilitation treatment after ischemic stroke at Institut Guttmann.

4.5.1 Study participants

Ischemic stroke patients with cognitive impairments in main functions involved in ADLs (attention, memory, executive functioning undertaking cognitive rehabilitation treatment in GUT by means of GNPT platform.

4.5.2 Inclusion criteria

Participant is willing and able to give informed consent for participation in the study, if not able to give informed consent it will be provided by a representative. Male or Female, aged 18 years or above.

4.5.3 Exclusion criteria

Patients not able to follow motor rehabilitation.

4.6 Study procedures

The main procedures involved in the study are integrated to standard care in motor rehabilitation treatments at GUT.

4.6.1 Recruitment

Participants will be identified by their internal (anonymized) idPatient, interventions addressed in this study as part of standard motor treatment will be supported by the PRECISE4Q predictive models therefore patients recruitment will be as in usual treatment.

4.6.2 Regulatory clearance

Clinical studies at GUT require an initial approval by Research and Innovation Committee (RIC) where the study protocol is presented and evaluated, after acceptance RIC decides if the study requires Ethical Committee approval (EC).
EC reviews the study protocol, the Study Informative Sheet (SIS), the Informed Consent (IC) and the Informed Questionnaire (IQ) of the study.
The Study Informative Sheet explains the study to the participants, the expected effects, possible complications (if exist) , what the study implies to the patient.
In the Informed Questionnaire of the study several questions are asked to the participant to assess if he/she understood the informed Consent and its implications.
In case of legal incapacity, a representative or tutor of the patient will sign SIS, IC and IQ.

4.6.3 Baseline assessments

Baseline assessments involve standard functional assessment scales e.g. Standard motor assessment scales The National Institutes of Health Stroke Scale (NIHSS), the Functional Independence Measure (FIM) (Upper body dressing) and Head Injury Behaviour rating scale (HIBS) .

4.6.4 Data management

The data referred to in this study is taken as part of the standard rehabilitation treatment with the results accessed by the research team.

4.6.5 Withdrawal of participants

During the course of the study a participant may withdraw early from it at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary. Provide justification for any procedures and observations that will be required following a complete withdrawal.
Ensure that the appropriate information on these arrangements is included in the participant Informed Consent.

4.6.6 Definition of the end of the study

As described in T5.5 end of study is planned for M36 (April 2021)

4.7 Study Intervention

Primary objective of the intervention is to obtain deficit reductions in motor functions regarding global upper limb response (pre-post treatment global difference The National Institutes of Health Stroke Scale (NIHSS), the Functional Independence Measure (FIM) (Upper body dressing). The intervention is based in the treatment selection of sessions (e.g. number of sessions per week, total number of sessions, total treatment duration, types of activities, etc) identified by predictive models generated during M13-M24 period and performed during the M24-M36 period (April 2020- April 2021).
Secondary objective of the intervention is to reduce levels of behavioural disorders (HIBS scale) after treatment. The intervention is based in the treatment selection of tasks obtained from predictive models generated during M13-M24 period and performed during the M24-M36 period (April 2020-April 2021).

4.8 Statistical analysis

Statistical comparisons involving intervention group and previous upper limb rehabilitation treatments (patients presented in Table 1 of this document).

4.8.1 Description of statistical methods

Pre-post statistical comparisons involving demographic variables (e.g. age, gender, level of education, time since injury), treatment data (e.g. number of sessions per week, total number of sessions, total treatment duration, types of activities (examples of such activities are occupational therapy, daily living activities performed by Nursery, Integral movement activities, etc) and standard upper limb assessment scales (e.g. NIHSS scale).

4.9 Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the Ethical regulations, following clearance described in section 3.6.2

5 Reintegration phase: Clinical study #3 Community integration based on psychosocial risk model

Community reintegration is defined as a person's return to everyday functional activities, instrumental activities of daily living, recreational and social activities, and interactions with family members and others. Social inclusion in the community is an important component of the quality of life that can be conceptualized as the fulfilment by the individual of culturally appropriate roles and responsibilities in society. Neurological disabilities such as stroke can alter roles between family members, peers, co-workers or school. The (re) integration into the community, which returns the individual to life in the community and "normalizes" the functioning and social participation, is a central goal of rehabilitation, therefore we propose the following interventional study based on predictive models obtained during rehab and reintegration data.

5.1 General information

Study Title	Early predictors of Community Integration among Individuals with Ischemic Stroke Living in the Community		
Clinical Phase	Rehabilitation and Community setting		
Design	Prospective longitudinal cohort study / Interventional		
Participants	Ischemic stroke patients		
Sample Size	200 for building predictive models 50 for interventional study		
Planned Period	2007-2019 for collecting dataset for building predictive models M13-M24 for building predictive models using the collected dataset M24-M36 (April 2020- April 2021) for interventional study		
Planned Recruitment period	M24-M36 (April 2020-April 2021)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Identify short, mid and long-term risk and protective factors associated to social integration (Identify psychosocial trajectories)	Institut Guttmann Sociofamiliar Assessment Scale – Rehab setting Community Integration Questionnaire – Community setting	End of rehab phase
Secondary	Promote tailored interventions during the rehab phase based on different identified psychosocial trajectories	Institut Guttmann Socio-familiar Assessment Scale – Rehab setting	Admission Discharge Comprehensive follow-up evaluations

5.2 Background and rationale

Due to advances in research medicine an increasing number of people with stroke are now returning to the community (Wood et al., 2010). In the context of stroke, community reintegration can be defined as a person's return to everyday functional activities, instrumental activities of daily living, recreational and social activities, and interactions with family members and others (Pang, et al. 2007). It is, therefore, a relatively broad concept concerned with participation in various life domains. The motor, sensory, perceptual or cognitive deficits, in addition to environmental and personal factors, lead to disability, hindering functional capability. Disability in the context of the current study is based on the International Classification of Functioning, Disability and Health model and refers to the inability to function in multiple life areas such as walking, taking a bath, working, going to school or work, accessing social services – it is seen as a result of an interaction between a person and their environmental and personal factors (WHO 2001/2002). Motor deficits are among the most common deficits that hinder a person's ability to complete their activities of daily living (ADLs) (Langhorne, Coupar & Pollock 2009) and can also affect the upper limb leading to poor functional use of the arm (Lo et al. 2010). This leads to problems while engaging in ADLs and community activities (Pang, Harris & Eng 2006). These limitations are not only for severe stroke because even after a mild stroke, ADLs and social roles may be affected (Rochette et al. 2007) and this may lead to participation restrictions.
Stroke survivors report problems with activity limitations and participation restrictions (39% to 65%) that are related to their community reintegration (Pang, Eng & Miller 2007). A Canadian study by Mayo et al. (2002) also showed that 50% of stroke survivors return to their communities to live with impairments that would not be manageable without the assistance of an able-bodied caregiver at home. This means that the individuals with stroke sequelae will have limited activities because of dependence and this may result in inactivity-related deconditioning leading to decreased physical capacity (Langhammer, Lindmark & Stanghelle 2007). This is aggravated by the fact that most stroke survivors are discharged from the hospital when they remain dependent for ADLs. This lack of independence would also lead to lower levels of community reintegration and poor quality of life (QOL).
Social inclusion in the community is an important component of the quality of life that can be conceptualized as the fulfilment by the individual of culturally appropriate roles and responsibilities in society. Neurological disabilities such as stroke can alter roles between family members, peers, co-workers or school. The (re) integration into the community, which returns the individual to life in the community and "normalizes" the functioning and social participation, is a central goal of rehabilitation. Literature about social inclusion after the acquisition of a neurological disability such as the stroke suggested that areas related to the greatest needs include aspects related to functionality and physical problems, mobility, transport, environmental barriers, problems related to the workplace and / or education.
There has been no prior research on stroke survivor trajectories associated to psychosocial outcomes such as social integration in the community setting. Therefore, the identification of specific trajectories and associations would be helpful for developing more tailored interventions for survivors and caregivers within the first year after the stroke onset.

5.3 Objectives and outcomes measures

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective Identify short, mid and long-term risk and protective factors associated to social integration (Identify psychosocial trajectories)	Institut Guttmann Sociofamiliar Assessment Scale – Rehab setting Community Integration Questionnaire – Community setting	End of rehab phase
Secondary Objectives Promote tailored interventions during the rehab phase based on different identified psychosocial trajectories	Institut Guttmann Sociofamiliar Assessment Scale – Rehab setting	Admission Discharge Comprehensive follow-up evaluations

5.4 Study design

Retrospective longitudinal cohort study and interventional study.

5.5 Participants description

In this section we describe the main characteristics of participants,

5.5.1 Study participants

Ischemic stroke survivors that performed the rehabilitation process at Institut Guttmann and afterwards are followed at the outpatient clinic with the scheduled comprehensive follow up assessment.

5.5.2 Inclusion criteria

Participant is willing and able to give informed consent for participation in the study, Male or Female, aged 18 years or above.
Individuals with an ischemic stroke who have completed the Institut Guttmann Sociofamiliar Assessment Scale both at admission and at discharged and the Community Integrations Questionnaire (CIQ) at the follow-up comprehensive evaluation will be included in the study.

5.5.3 Exclusion criteria

Individuals with an ischemic stroke who have not completed the Institut Guttmann Sociofamiliar Assessment Scale both at admission and at discharged and the Community Integrations Questionnaire (CIQ) at the follow-up comprehensive evaluation will be excluded in the study.

5.6 Study procedures

The main procedures involved in the study are integrated to standard care in rehabilitation treatments at GUT, in reintegration phase the main procedures are those involved in GUT's Comprehensive follow-up evaluations.

5.6.1 Recruitment

Participants will be identified by anonymized idPatient, interventions addressed in this study as part of standard rehabilitation/follow up, will be supported by the PRECISE4Q predictive models therefore patients recruitment will be as in usual rehabilitation/follow up treatments.

5.6.2 Regulatory clearance

Clinical studies at GUT require an initial approval by Research and Innovation Committee (RIC) where the study protocol is presented and evaluated, after acceptance RIC decides if the study requires Ethical Committee approval (EC).
EC reviews the study protocol, the Study Informative Sheet (SIS), the Informed Consent (IC) and the Informed Questionnaire (IQ) of the study.
The Study Informative Sheet explains the study to the participants, the expected effects, possible complications (if exist) , what the study implies to the patient.
In the Informed Questionnaire of the study several questions are asked to the participant to assess if he/she understood the informed Consent and its implications.
In case of legal incapacity, a representative or tutor of the patient will sign SIS, IC and IQ

5.6.3 Baseline assessments

Institut Guttmann Sociofamiliar Assessment Scale – Rehab setting
Community Integration Questionnaire – Community setting

5.6.4 Data management

Data referred to in this study is taken as part of the standard rehabilitation treatment with the results accessed by the research team.

5.6.5 Withdrawal of participants

During the course of the study a participant may withdraw early from it at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary. Provide justification for any procedures and observations that will be required following a complete withdrawal.
Ensure that the appropriate information on these arrangements is included in the participant Informed Consent

5.6.6 Definition of the end of the study

As described in T5.5 end of study is planned for M36 (April 2021)

5.7 Study Interventions

We plan to develop an intervention focused on empowering individuals facing needs and demands that probably they will have to address after discharge from rehabilitation services and back to the community. This intervention will be based on psychosocial trajectories previously identified. Those

who belong to psychosocial risk trajectories will benefit from a newly implemented intervention that aims to support stroke survivors' community integration during the first months following hospital discharge.
The intervention will be developed during the rehabilitation process with around 50 individuals with ischemic stroke classified as FRAGILE in relation to the psychosocial trajectories.
The intervention will promote connections with community resources such as associations in order to prevent problems with activity limitations and participation restrictions (e.g. provided by means of GUT's SIIDON platform (https://siidon.guttmann.com/es).
Intervention will also address meaningful activities, professionals can do this by using questions which explore what stroke perceive to be the significant barriers, and what skills and supportive networks are needed.
The intervention will also emphasize the importance of rehabilitation practitioners supporting stroke survivors' to engage with meaningful self-selected social activities and the importance of stroke survivors having the freedom and autonomy to set their own goals. It will furthermore focus on promoting positive attitudes. Being hopeful, determined, resilient and courageous is an essential part of pursuing their self-selected valued activities. Acknowledging and encouraging the importance of these behaviors and attitudes should be promoted during rehabilitation.
Social and environmental risk factors that will be assessed during the intervention include:
Self-care attitudes
Social network
Vocational and ocupational difficulties (lack of financial resources)
Living arrangements
Mobility (the need for personal and transportation assistance)
Family dynamics

5.8 Statistical analysis

5.8.1 Description of statistical methods

Pre-post statistical comparisons involving demographic variables (e.g. age, gender, level of education, time since injury), Institut Guttmann Sociofamiliar Assessment Scale – Rehab setting
Community Integration Questionnaire – Community setting
Latent class growth mixture modeling will be used to determine psychosocial trajectories. Multinomial regression analyses will be used to predict trajectory membership. Potential predictors will be demographic, stroke-related, and neuropsychological factors.

5.9 Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the Ethical regulations, following clearance described in section 3.6.2.

6 Conclusions

This deliverable presented the activities to be conducted in order to achieve objective 2 of WP5 (Clinical Studies for Model Validation).

Objective 2 aims to design and conduct a clinical validation study for rehabilitation/reintegration phases, this document addresses the study design, described in T5.4 during M1-M12 period. The clinical validation will be executed as described in T5.5 (M13-M36 period) and will be reported in D5.5. deliverable.

This document presents three main sections: first a general description of the clinical study protocol and then the tailoring of the protocol to 1) the rehab phase and 2) the follow up phase. The main questions to be addressed within the validation studies are described in deliverable D4.1 (White paper on stroke risk, health and resilience factors).

Therefore clinical validation studies described in this document take as starting point the use cases defined in deliverable D4.1 for rehabilitation and follow up phases. Specifically we propose 3 studies (studies #1 and #2 for rehabilitation phase and study #3 for reintegration phase):

1- Cognitive training using Gutmann NeuroPersonal Trainer database with the intervention obtained from predictive models that will provide new Neuro Rehabilitation Ranges and optimal number of sessions, tasks, treatment durations (as well as other relevant parameters described in D4.1).

.2- Functional upper limb training involving physical therapy with the intervention obtained from predictive models that will provide us optimal treatment durations, optimal number of sessions of occupational therapies, movement therapies or AVDs activities.

3- Community integration based on psychosocial risk model, intervention here is performed during rehabilitation phase (early interventions addressed during rehabilitation phase are expected to produce an impact in reintegration phase). It will be based in the risk trajectories that will be identified by the predictive models involving main community integration assessments.

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