Study protocol for Randomised Double Blinded Controlled Trial with a longitudinal design monitoring effect of COMprehensive Intensive REhabilitation Program after STROKE (COMIRESTROKE)

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1. Introduction

Ischemic stroke is one of the leading causes of neurological dysfunction, the most common being motor disability which negatively impacts quality of life and active participation (1, 2). There is evidence supporting the positive influence of rehabilitation in well-coordinated multidisciplinary stroke units (3) where physiotherapy (PT) plays an indisputable role in impairment reduction, activity independence, social participation and quality-of-life improvement (4). On the other hand, clear evidence concerning the effectiveness of different PT approaches as part of rehabilitation is still lacking. Several large intervention trials have reported that participants' motor performance increased. Nevertheless, this was enhanced to a similar extent for both the intervention and control groups in most trials (5). Small beneficial differences between groups could be caused by a non-systematic/accidental indication of PT methods in rehabilitation processes. Research from other areas also suggests that between-group differences in improvement may be found on an item level of multi-item measurements even in cases when they are not observed on the total scores, and thus, a more detailed item-level analysis may provide an important insight (6, 7).

Many PT techniques have been developed to facilitate the recovery of motor disability in patients after stroke (3, 8-10). All are related to neural plasticity via the development of new neuronal interconnections, acquiring new functions, and compensating for impairment (11), but they explain little in relation to the mechanisms underlying motor recovery heterogeneity. Physical activity training acts as an acute stress that enhances neurobiological processes such as activity-dependent plasticity, learning and memory. Motor/skill acquisitions and technology based PTs systematically train damaged function by the repetition of new and complex movements, which induces a substantial cortical network reorganization closely related topographically to the trained movement which leads to synaptogenesis (12). Neuroproprioceptive "facilitation, inhibition" (neurofacilitation) PT enhances the effectiveness of the synaptic connections among neurons forming functional networks, which leads to the evocation of movement by some otherwise weak and insufficient stimuli. A suitable combination of afferent stimuli modulates interneuronal systems, repeatedly activates motor programs at the subcortical level, and as such induces adaptive and plastic processes of the CNS (13). We are convinced that to prevent maladaptive plasticity, and maximize functional gain in patients with stroke, individualized therapeutic goals, should be considered. The ICF model proposes a comprehensive, biopsychosocial approach to patients, setting personalised goals based not only on diagnosis but also on the patients´ functional status and activities. It has been recommended by the World Health Organisation (WHO) (14), and was globally agreed-on as a conceptual framework and common language to document and code functional status information (15, 16). However, to date the basis of such a personalised approach to ischemic stroke (IS) therapy has not been clearly clarified, described and confirmed yet. This clinical trial will address this gap in IS rehabilitation as follows using a

three-pronged approach to the COMprehensive Intensive REhabilitation Program after STROKE (COMIRESTROKE): **COMIRESTROKE – ICF**, the mostly individualized approach implementing the International Classification of Functioning, Disability and Health (ICF) model with aim to improve an individual's recovery (rather than impairment) through effective management of care (14); **COMIRESTROKE – TECH**, approach implementing technology-based PT" and **COMIRESTROKE – NEFI**, approach implementing neuroproprioceptive "facilitation and inhibition" PT.

There is very limited evidence to guide judgements regarding the rehabilitation potential following stroke (17-20). Research shows that some clinical features such as the level of consciousness, severity of hemiplegia, incontinence, dysphagia and dysphasia (21) or disease severity (22, 23) may be considered as indicators as to whether the rehabilitation process could be effective. However, confusion between predicting natural unassisted recovery and predicting responsiveness to targeted rehabilitation still remains (17). Moreover, prediction models of rehabilitation potential have never been fully and properly prospectively tested. The models considered by Prabhakaran et al., 2008 were only able to explain 47% of the variance in recovery after stroke with 53% of the variance remaining unaccounted (24). Nowadays focus shifted from the determination of rehabilitation potential to identifying clear indicators of effective rehabilitation including molecular biological readouts (25). This is reason why a wide range of patient characteristics will be collected. We consider, the patients´ subjective feelings about how they have improved to be the most important aspect. Therefore, the Goal Attainment scale (GAS) together with the Patient-reported Outcomes Measurement Information System (PROMIS) Global Health, and the World Health Organization Disability Assessment Schedule (WHODAS 2.0) were chosen as **primary outcomes**. As **secondary outcomes**, measurements will be taken of motor, cognitive, psychological, speech and swallowing functions as well as functional independence.

Moreover, focus will be placed on the identification of novel biological molecules reflective of effective rehabilitation by **molecular assessment**. **Long non-coding RNA** (**lncRNA**) are defined as RNA transcripts >200 nucleotides with limited coding potential (26). They have been classified into anti-sense, intronic, large intergenic, promoter associated and UTR-associated lncRNAs (27). They are involved in vital cellular regulation (28) including genomic imprinting (29), epigenetic chromatin modification (30), transcriptional interference (31) and nuclear export (32). **Importantly, lncRNAs determine nervous system development** (33). A majority of lncRNA display specific expression within neuroanatomical regions (34). Many of these lncRNAs display genomic localizations in close proximity to known neurodevelopmental regulators (35). This has led to the general hypothesis that the expanded diversity in lncRNAs is pivotal to the higher order cognitive ability of humans. **Long non-coding RNAs as promising therapeutics biomarkers in IS:** LncRNAs regulate key factors involved in ischemic/reperfusion injury eg. calcium overload (Chen et al 2019). Excessive calcium accumulation results in the activation of calcium/calmodulin-dependent protein kinase II (CaMKII), a family of serine/threonine kinases involved in IS pathogenesis (36). CaMKII is controlled by lncRNA *C2dat1*. Elevated levels of lncRNA *C2dat1* have been identified in both *in vitro* and *in vivo* models of IS (36). Studies showed that IS injury leads to increased glutamate release activating N-methyl-D-aspartate (NMDA) receptors which initiate cellular apoptosis (37). Overexpression of lncRNA *GAS5* increased the apoptotic rate in neurons with its administration resulting in a greater area of cerebral infarction in animal models (38). It has been suggested that inhibition of the lncRNA *GAS5* could potentially reduce apoptosis and infarct size in IS leading to improved neurological functioning. Evidence has pointed to lncRNA moderation of autophagy, angiogenesis and oxidative stress caused by IS. Exploring lncRNAs involved in such processes will assist in understanding the recovery networks induced by IS rehabilitation approaches.

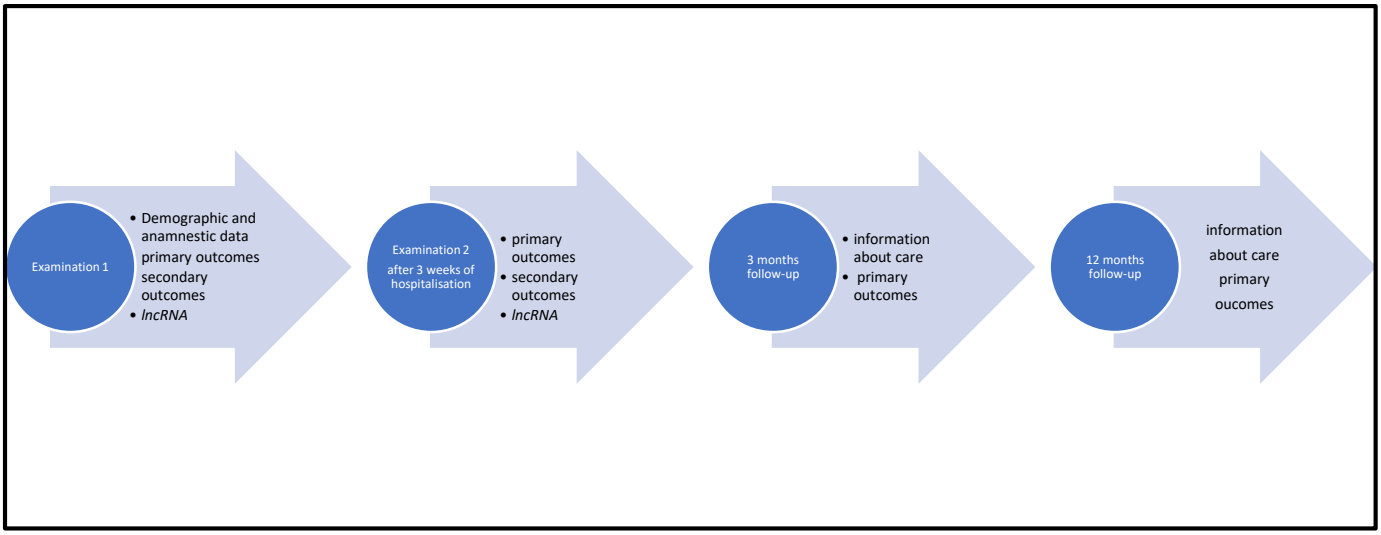
2. Participants and methods

2.1. Clinical trial design

This will be a Four-Arm Parallel-Group Randomised Double Blinded Controlled Trial with a longitudinal design. Patients who fulfilled inclusion criteria will be randomly assigned to one of the four research groups (Group 1, 2, 3 or 4). Three groups will undergo an inpatient COMIRESTROKE (4 hours/day for 3 weeks). Group 1 (COMIRESTROKE – ICF) will undergo individualised rehabilitation therapy embodying the ICF system as a therapeutic tool, where current needs and wishes of the person after IS are integrated into an interdisciplinary team rehabilitation programme management. Group 2 and 3 will undergo a standard comprehensive intensive rehabilitation program three hours per day (39) plus one hour of specific PT (an individual neuroproprioceptive "facilitation inhibition" for Group 2, a technology-based training for Group 3). Group 4 will undergo standard care and will serve as comparative one to the intensified intervention groups.

Participants will be examined four times (Figure 1). At the beginning and after three weeks of hospitalization (both primary, secondary outcomes and a blood draw will be obtained for total RNA extraction, cDNA synthesis and real-time QPCR assessment of lncRNA candidates previously identified as potential therapeutic influencers in ischemic stroke), and then three months and one year after the end of the program (primary outcomes only).

Figure 1: Design of the study



2.2. Eligibility criteria and subgroups

Participants will be identified by specialists in neurology and rehabilitation from inpatients at the Department of Acute Care, Department of Neurology, Thomayer University Hospital or University Hospital Kralovske Vinohrady, Prague, Czech Republic.

Inclusion criteria: Adults (18 – 85 years) after the first ischemic stroke in early sub-acute phase (40, 41), with a slight to moderately severe disability [2 – 4 on the Modified Rankin Scale (42)],

with minimal or moderate motor deficit of upper or lower extremities (on NIHSS Item 5 or 6 scores 1–3 points) who were able to perform activities of daily living prior to stroke event [0 – 2 on the Pre-Stroke Modified Rankin Score (43)], with a potential to accept 4 hours of comprehensive rehabilitation per day and to profit from the physiotherapy. Czech is their native language or its knowledge is at the level of the mother tongue.

Exclusion criteria: Low level of consciousness (vegetative state and/or minimally conscious state); severe cognitive decline that would interfere with administration of the tests, premorbid illiteracy, severe visual and/or auditory deficit that would prevent proper completion of the tests; behavioural disorders and/or lack of cooperation with therapist; and severe medical problems with a poor prognosis, (e.g., severe frailty, advanced and incurable cancer, fracture, cardiovascular disorders as chronic heart failure NYHA III, IV, symptomatic coronary artery disease Angina Severity Class III, IV, respiratory insufficiency as chronic obstructive pulmonary disease GOLD IV, and other severe disease) (44).

Randomisation
All patients meeting the above criteria will be invited to participate and asked to provide a written informed consent. They will be randomly assigned (1:1:1:1) as soon as possible, but always within 48 hours of admission, into one of the four interventions (represented by Group 1, 2, 3 or 4) using offsite-independent randomization protocols (www.randomization.com). Concealed allocation will be performed using sequentially numbered opaque sealed envelopes only accessible by research personnel with no involvement in the trial.

2.3. A detailed description of four groups

Three groups in intervention cohorts will receive the same length of rehabilitation, i.e., 4 hours per day. Therapists in each group will be maximally helpful and will adopt a schedule for each patient to complete all the sessions. The treatment in each session will be led in person by well-educated, experienced therapists specially trained in each method. The treatment will be modified according to the patient´s status and reaction to the therapy. Physical load during all therapies will be perceived maximally as a moderate level of intensity [12 - 14 on the Borg Scale (45)]. Information about the treatment will be recorded using codes of Public Health Insurance, Czech Republic (codes correspond to The Current Procedural Terminology code set system).

Group 1: COMprehensive Intensive REhabilitation Program after STROKE implementing the ICF concept (COMIRESTROKE – ICF)

This interventional arm suits the purposes of setting individual goals of the therapy which take account of the given situation of the rehabilitated person (46-48). The ICF system establishes a common health language to articulate human functioning across the lifespan and from individual to population health settings system (49, 50). On the individual level, functioning is considered as an interaction between a health condition and the contextual factors facilitating or acting as a barrier for functioning (51). Focusing on patient's quality of life and participation domain of the ICF applies a paradigm shift in neurorehabilitation research design (52). Engagement in valued activities was found to be significantly associated with subsequent improvement in emotional well-being (53) .
Patients randomized to the GROUP 1 will undergo a multidimensional assessment, a functional profile will be created and the individual goals and intervention proposed and defined throughout the ICF framework. Clinical application can be rather arduous (54) and sharing of the feasibility experience is highly valued. This study arm design follows recommendations and

experience with implementation of the ICF model into clinical practice in rehabilitation in people after stroke (55).
Limiting the burden of iterative processing the proposed battery of clinical examinations, questionnaires surveys and filling out the ICF core set documentation which is then used to compile "ICF Categorical Profile", this study proposes a direct linking of some clinical test results to the codes included in the Comprehensive ICF core set for stroke used (56). Linking of normal-range clinical examination results may ease the procedure. Linking will take place regarding specified items from the test battery: WHODAS 2.0 (57) NIHSS, mRS, MoCA (58), MAL (59), FIM, BBS (60), TUG, NHPT, ARAT, GSS, 3F test, MAST. Overlapping items will be further discussed.
The clinical assessment involves the following three steps: 1) description of patient's problems and resource; 2) setting of mutually agreed goals, based on the functional profile; 3) and determination of intervention targets. The interdisciplinary team together with the patient will use the functional profile to define in detail the overall goal and sub-goals, and to determine specific therapeutic interventions to achieve them (42). Participants in this group will undergo four hours of treatment per day (the same time as in the remaining two cohorts), but the time spent with each specialist will depend on the individually set goals. The "ICF Intervention Table" will be used to monitor and evaluate the work during individual targeted interventions and will also serves as a means of communication between the members of the interdisciplinary team. The team will meet weekly to provide feedback, evaluate the fulfilment of the set goals and to adjust therapeutic procedures so that the goals of the therapy are best met.
After the end of the intensive complex inpatient program COMIRESTROKE – ICF, as the continuum of care, participants will be referred and to a short-term outpatient rehabilitation programme.

Group 2 and 3

Participants will undergo COMprehensive Intensive REhabilitation Program after STROKE routinely offered at the Department of Rheumatology and Rehabilitation, Third Faculty of Medicine, Charles University and Thomayer University Hospital (39) three hours per day. In the program, the multidisciplinary team of practitioners from different clinical fields (physiotherapy, occupational therapy, clinical speech therapy and psychology) will be led by a medical doctor, a specialist in rehabilitation and physical medicine. Efforts of the different team members are parallel and discipline oriented.

In addition, participants in these two groups will undergo one hour of physiotherapy per day.
Group 2: COMprehensive Intensive REhabilitation Program after STROKE implementing technology-based physical PT (COMIRESTROKE – TECH) Participants will receive a technology-based PT that follows the principles of sensorimotor learning, i.e. repeated specific and targeted functions in different environments / conditions in order to strengthen the memory footprint and initiate structural changes in the CNS. According to the indication, participants will be offered one of the robotic systems using an exoskeleton (Gloreha, Erigo and Meditutor) or a therapy using a virtual environment (61, 62).

Group 3: COMprehensive Intensive REhabilitation Program after STROKE implementing neuroproprioceptive "facilitation and inhibition" physiotherapy (COMIRESTROKE – NEFI). Participants will receive an individual neuroproprioceptive "facilitation, inhibition" PT (Vojta reflex locomotion, Bobath concept), where appropriate stimuli in a suitable time sequence are combined with the aim to maintain optimal motor pathway function and ability control (63, 64).
After finishing this intensive complex inpatient program COMIRESTROKE, participants will undergo standard/not directed treatment offered by the Czech Health Care system. Information

as to the health and social care the rehabilitant received after hospitalisation will be collected by phone call.

Group 4: A comparative group will undergo standardly provided care at department of neurology including face to face physiotherapy (bed mobility, transfers, gait, therapeutic exercises, positioning, education).

2.4. Pre- and post-intervention assessments

Once an informed consent is obtained prior to randomisation; participants will be referred to study examiners - a Physical Medicine and Rehabilitation physician, a neurologist, a physical therapist, an occupational therapist and a psychologist, who will not know the treatment group of the patient. They will administer baseline testing during the 2nd and 3rd day after admission to the department (Pre-assessment). The Post-assessment 1 will be done at the end of the three-week inpatient intensive comprehensive rehabilitation (during the last two days of hospitalization). Follow-up assessments will take place 3 and 12 months after the admission, respectively, by a telephone interview and hospital visit for blood draw. The aim is to be assessed only by one examiner, in case of more examiners, inter-rater reliability will be assessed (Table 2).

Table 2: Timing and distribution of examination in the team

test	abbreviation	Inclusion and exclusion criteria	Examination No			
			1	2	3	4
			baseline	+3 weeks	+3 months	+ 1 year
Neurologist						
Demographic and anamnestic data (age, after first ischemic stroke, days after the stroke)		x				
Demographic and anamnestic data (weight and height, cardiovascular risk factors, Bamford classification, medication)			x			
Modified Rankin Scale	mRS	x		x		
Pre-Stroke Modified Rankin Score	pre-stroke mRS	x				
Historic Stroke Motor Severity Score	HSSS	x				
National Institute of Health Stroke Scale	NIHSS	x				
Psychologist*						
Montreal Cognitive Assessment	MoCA		x			
Amnesia Light and Brief Assessment	ALBA		x	x		
NEO-Five Factor Inventory	NEO - FFI		x			
Patient-reported Outcomes Measurement Information System Global Health	PROMIS		x	x	x	x
the World Health Organization Disability Assessment Schedule	WHODAS		x	x	x	x

the Goal Attainment scale	GAS					
Picture naming and immediate recall	PICNIR		x	x		
Neuro - QOL depression			x	x		
physical therapist						
Hand Dynamometer			x	x		
postural tremor			x	x		
Action Research Arm Test*	ARAT		x	x		
Motor Activity Log*	MAL		x	x		
Timed Up and Go*	TUG		x	x		
Berg Balance Scale*	BBS		x	x		
The 10 Metre Walk Test*			x	x		
The 6 Minute Walk Test*			x	x		
Functional Independence Measure*	FIM		x	x		
Laterality index	LI		x			
Nine Hole Peg Test			x	x		
speech therapist*						
The Gugging Swallowing Screen	GSS		x	x		
The 3F Test – Dysarthric Profile	3F test		x	x		
Dysan			x	x		
The Mississippi Aphasia Screening Test	MAST		x	x		
Image Naming Test	INT		x	x		
Blood – Total RNA extraction cDNA synthesis lncRNA assessment (*C2dat1, GAS5, MALAT1, PARTICLE, H19, MEG3*)			x	x		

*Tests recommended by General Health Insurance (GHI), Czech Republic.

The qualitative data will be collected in semi-structured interviews with patients as well as clinical specialists with the aim of capturing an extended health evaluation. Specialists will have the possibility to look at the hospital information system, or search in the National Register of Paid Health Services. Data will be captured using an electronic Case Report Form (eCRF) (65).

The following data will be collected:

Demographic and anamnestic data including personal factors (sex, age, education, occupation, social relations, living situation), weight and height, laterality index (66), number of days after the stroke event, personality based on the NEO-Five Factor Inventory (NEO-FFI) (67), pre-stroke functional status based on modified Rankin Scale (68), cardiovascular risk factors (69), the degree of neurological impairment according to the National Institute of Health Stroke Scale (70) and disability with the Modified Rankin Scale (42), Bamford classification of IS based on the initial presenting symptoms and clinical signs (71) as well as pharmacotherapy.

2.5. Outcomes and measures

2.5.1. Primary Outcomes

- PROMIS Global Health is a 10-item scale which asks the patient to assess (self-report) their physical, mental and social health in the past 7 days (72, 73).

- WHODAS 2.0 is a generic assessment instrument developed by WHO to provide a standardized method for measuring health and disability. It is grounded in the conceptual framework of the ICF and integrates an individual's level of functioning in major life domains and directly corresponds with ICF's "activity and participation" dimensions. The 36-item version will be used. Higher score means higher disability (74).

- GAS is an individualized outcome measure involving goal selection and goal scaling that is standardized in order to calculate the extent to which patient's goals are met. Each goal is rated on 5-point scale (-2 much less than expected, 0 achieved the expected level, 2 much more than expected (75, 76).
  Three types goals will be established:
  A. Overarching long-term goal (Global Goal, G) that reflects a desired improvement on the level of participation: usually restoration of previous life including remunerative employment, sport and leisure activities (interview by call at 3 and 12 months follow up).
  B. Mid-term goal (Program Goal, P) that reflects improvement mainly in the domain of activities and participations achievable by the rehabilitation program: restoration of self-care, (almost) independence in daily living etc. (interview by call at 3 months follow up)
  C. Three Short-term goals (Cycle Goals C1, C2, C3) mainly in the domain of functioning and activities. Usually specific, most problematic components of the Program Goal (evaluated by the rehabilitation team together with the rehabilitant).

2.5.2. The secondary outcomes

The secondary outcomes include clinical tests and questionnaires of physical functions and functional independence (examined by an independent physical therapist), speech and swallowing (examined by an independent speech therapist), cognitive and psychological functions (examined by an independent clinical psychologist).

2.5.2.1. Physical functions and functional independence

Upper extremity functions

- Jamar Hydraulic Hand Dynamometer will be used to measure isometric grip force from 0-90 kg. Five handle positions from 35-87 mm will be tested. The measurement is in kg (the higher the value, the better the function) (77).

- A postural tremor will be measured by the 3-axis accelerometer and 3-axis gyroscope chip (Motion Tracking sensor MPU-6050) which can measure acceleration up to 16 g and rotation up to 2000 degrees per second. The sensor will be fixed to the patient using a ring on a finger during stretching the whole arm forward, separately passed for the left and right hand and with opened and closed eyes (one-minute measurement for each position). Data from the chip will be acquired by an own measuring device with microcontroller Atmel Mega 328 and stored on an SD card.
  For the signal analysis, the magnitude of acceleration – the root of sum of each component squares – will be computed from separate axes. The sampling frequency will be 100 Hz. Thus, four signals with 6000 samples will be recorded for each patient – records of postural tremor for right/left hand with opened/closed eyes.
  For each record, the signal of acceleration will be filtered by a filter of isoline (typically by high-pass 2^{nd} order Butterworth filter with cut-off frequency of 0.5 Hz). Consequently, the power spectral density (PSD) will be estimated.
  The spectral characteristic will be parameterized by selected parameters, for example f_{MAX} (a frequency for which the smoothed PSD is maximal - lower value, lower tremor) or $P_{f1\text{-}f2}$ (a power of the signal in band from f_1 to f_2 - lower value, lower tremor) (78).

- Nine Hole Peg Test is used to measure finger dexterity. A client takes the pegs from a container, one by one, and places them into the holes on the board, as quickly as possible. Shorter times reflect better function (79).

- Action Research Arm Test (ARAT) is a 19 item observational measure to assess upper extremity performance (coordination, dexterity and functioning). Items are categorized into four subscales (grasp, grip, pinch and gross movement). A higher score means better function (80).

- Motor Activity Log is a scripted, structured interview to measure real-world upper extremity function consisted of 14 activities of daily living such as using a towel, brushing teeth, and picking up a glass. A higher score means better function (81).

Mobility and walking

- Timed Up and Go is a simple performance-based measure of dynamic balance. The subject stands up from a chair, walks 3m, turns back, and sits down again as quickly and safely as possible while being timed. Shorter times reflect better mobility (82).

- Berg Balance Scale is a 14-task scale that requires subjects to maintain their balance in positions and tasks of increasing difficulty. A lower score means worse balance (83).

- The 10 Metre Walk Test is a performance measure used to assess walking speed in meters per second over 10 meters. Shorter time reflects better mobility (84).

- The 6 Minute Walk Test is a long walking capacity test recording the maximal distance a subject can walk at the fastest speed possible in 6 minutes. The more distance covered, the better the walking performance is (84).

Functional Independence

Functional Independence Measure is an 18-item measurement tool which explores an individual's physical, psychological and social function. It uses the level of assistance an

individual needs to grade functional status from total independence to total assistance. The higher the score, the better (higher independence) (85).

2.5.2.2. Speech and swallowing

The Gugging Swallowing Screen is a simple stepwise bedside screen that allows a graded rating with separate evaluations for nonfluid and fluid nutrition starting with nonfluid textures. It assesses the severity of aspiration risk. A higher score means better function (85).

The 3F Test – Dysarthric Profile consists of three subtests (Faciokinesis, Phonorespiration, Phonetics). The overall Index of Dysarthria (ID) is a sum of 45 items with the maximum score of 90 (the best function) (86).

Following the previously published guideline (87), the dysarthria assessment is based on the automatic evaluation of utterances, including sustained phonation, speech diadochokinetic task, and connected speech. Utterances will be recorded during the sessions with speech language pathologist. The recording will take place in a quiet room with low ambient noise using a head-mounted condenser microphone (Shure Beta 53, Niles, Illinois, U.S.), placed approximately 5cm from the mouth corner at an angle of 70°. The recordings will be sampled at 48kHz with 16bit resolution. The automatic analysis will be performed using the beta version of the freely available Dysarthria Analyzer (Czech Technical University in Prague, available at http://dysan.cz/).

The Mississippi Aphasia Screening Test (MAST) was developed as a brief, repeatable screening measure for individuals with severely impaired communication/language skills. It has nine subtests that range from 1 to 10 items per subscale. The Index scores sum to 50 points each and are added for the MAST Total Score (0 -100 points). The higher the score, the better function (88).

Image Naming Test (Test pojmenování obrázků, TPO) is a test of confrontational naming of nouns and verbs. Words are selected based on success, frequency of occurrence, age of adoption, length, and visual complexity. The maximum sum is 60 points (30 verbs and 30 nouns), the results can be assessed qualitatively according to the type of unexplained words (89).

2.5.2.3. Cognitive and psychological functions

The Montreal Cognitive Assessment (MoCA) is an assesment for detecting cognitive impairment ranged between 0 and 30 points. The more the better. The Czech version was validated and cut-offs and norms were established (90, 91).

The Amnesia Light and Brief Assessment (ALBA) is an original Czech and innovative test to assess more cognitive functions (therefore Assessment in the name) including memory (therefore Amnesia) easily (therefore Light) and quickly in three minutes (therefore Brief). The ALBA consists of four tasks: (1) repetition and encoding of a six-word sentence "Indian Summer Brings First Morning Frost", (2) sequential demonstration of six gestures and (3) their immediate recall, and (4) final recall of the original sentence. The first task of a sentence repetition reflects (1) language (impaired in aphasia) or (2) encoding and working memory (impaired in memory and attention deficits). The second task of gesturing can be impaired as a result of sensory aphasia or apraxia. Short-term and episodic memory is measured in two different ways, (1) in the third part of the ALBA, i.e., incidental memory of the gestures, and

(2) in the fourth part, i.e., intentional verbal memory of the sentence. Overall memory can be expressed as the ALBA score, which is a sum of correctly recalled sentence words and gestures. The higher scores of each ALBA part the better function. Scores of individual parts range from 0 (the worst) to 6 points (the best) for each of four tasks: (1) the number of correctly repeated words of the sentence (Word 1 score: 0–6 points), (2) the number of correctly recalled words of the sentence after the distraction using the TEGEST (W2 score: 0–6), (3) the number of correctly performed gestures of the TEGEST (Gesture 1 score: 0–6), and (4) the number of correctly recalled gestures of the TEGEST (G2 score: 0–6). The sum, called ALBA score, is derived from correctly recalled words of the sentence and correctly recalled gestures together (W2 + G2: 0–12 (6 + 6)). Example scores of the ALBA test can be the following: 5/1 + 5/3 (W1/2 + G1/2) that gives a total ALBA score: 4 (1 + 3) points (92, 93).

Picture naming and immediate recall (PICNIR) is an original Czech and brief test which is a method certified by Ministry of Health of the Czech Republic in 2017. The purpose of the PICNIR is to evaluate written speech, long-term sematic and short-term visual memory simultaneously and quickly in five minutes. The test consists of two parts. The task of an examinee is to write down names of 20 black and white pictures in one word and remember them at the same time. Then they are asked to rewrite as many picture names as they can recall during one minute. The results of the PICNIR include a number of wrongly named or unnamed pictures in the first naming part and a number of correctly recalled picture names in the second recall part. The less naming errors and more recalled picture names the better (94).

Neuro - QOL depression is a self-report of health-related quality of life in domain concerning depression (95). (72)

2.5.3. Other Pre-specified Outcome Measures - molecular biological readouts of rehabilitation

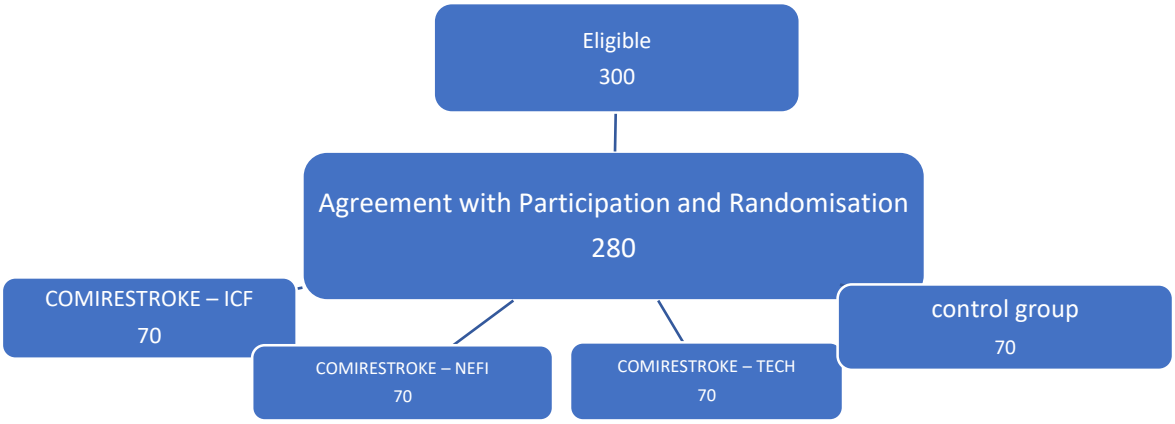
Blood will be taken for total RNA extraction, cDNA synthesis and real-time QPCR assessment of lncRNA candidates previously identified as potential therapeutic influencers in ischemic stroke. Whole blood will be collected from fasting patients for RNA analysis. A RiboPure™-Blood Kit (cat# AM1928, ThermoFisher Scientific) will be used for isolating high-quality RNA directly from whole blood. This kit contains an RNA*later*® Solution (cat.# AM7020, ThermoFisher Scientific) that protects RNA and is designed to eliminate the need to process samples as soon as they are harvested. RNA*later*® Solution also "freezes" the gene expression profile of the cells. Treated samples can be safely stored at ambient temperature for extended periods of time (up to three days or more). Blood samples stored in RNA*later*® Solution yield RNA of comparable quality to blood samples processed directly according to the commercial website. Expected average yields of total RNA will be between 2–4 µg/0.5 mL of whole blood. Total RNA will be reverse transcribed into cDNA. Human lncRNA and internal endogenous gene (eg. *GAPDH*) expression will be quantified using RNA extracted from blinded samples (ie. concealment of group allocation) to eliminate bias.

2.6. Estimated size

It is estimated that approximately 110 people will be recruited to the clinical trial each year. This number is based on the fulfilment of performance and quality indicators report of cerebrovascular care at the Centre for Highly Specialized Patient Care for Stroke Patients at Thomayer Hospital 2019. A total of 210 people is expected to be enrolled in the clinical trial over a period of two years (Figure 2), corresponding to a required sample number of 70 patients per group. This value is necessary in order to detect a significant difference in improvement

between two groups when achieving a mean difference effect (Cohen's d = 0.5), a significance level of α = .05 and a strength of 1-β = .80. The sample size was determined based on the minimal clinically significant change on a Berg balance scale (96).

Figure 2: Planned recruitment and randomisation process



2.7. Descriptive statistics

On the baseline, the distribution of all primary and secondary outcomes will be visualized using histograms and QQ plots. We expect normal distributions in most of the variables defined as raw scores from appropriate tests, or in their log transformations (e. g. tests measuring time needed to walk certain distance or to perform a task). The groups will be compared in their characteristics, primary, and secondary outcomes using the one-way analysis of variance (ANOVA), and its nonparametric version (Kruskal – Wallis test), where needed. The Benjamini-Hochberg correction (97) will be used to account for multiple comparisons. We expect no differences between groups on the baseline. If differences are observed, these will be accounted for in the longitudinal models.

2.8. Hypotheses

This clinical trial will test the following scientific hypotheses:

I. COMIRESTROKE under all three settings has a positive influence on all outcomes and higher effect than control group.
II. COMIRESTROKE - ICF will have the highest impact on primary outcomes (GAS, PROMIS, WHODAS 2.0) and on such secondary outcomes that were identified as treatment goals. Furthermore, we expect the highest impact on the primary outcomes in the follow-up (three and twelve months after finishing the rehabilitation).
III. COMIRESTROKE – NEFI will have the highest effect on the secondary outcomes, mainly on motor functions. Moreover, it will most significantly lead to the initiation of plastic and adaptive processes, assessed by the level of lncRNAs in the peripheral blood.

IV. The most important predictor of effective rehabilitation will be the level of disability at admission time; however, the content of the rehabilitation will have an impact on perceived, clinical, and physiological changes of the rehabilitant.

The exploratory goals of this clinical trial are as follows:
Goal I - Improvement patterns: Considering the high number of measured outcomes, for a deeper understanding of therapy efficacy with respect to patient and treatment characteristics, this clinical trial will aim to identify groups of patients with similar improvement patterns post therapy.
Goal II - Item-level analysis: To provide a deeper understanding of the differences in effectiveness between the three therapeutic approaches, this clinical trial will plan to explore item-level between-group differences in improvement.

2.9. Measuring the effectiveness of rehabilitation

To test hypothesis I., i.e., a positive influence on all outcomes, the effect of therapy for each therapeutic group will be assessed separately by paired t-tests performed on pre-test and post-test scores. The Wilcoxon rank test will be used on data where normal distribution cannot be expected.

To test hypotheses II. and III, a comparison between therapeutic groups will be performed using two sample Student t-tests on differences between measurement time points (or Wilcoxon tests respectively for data, where normal distribution of the differences cannot be expected). For hypothesis II, the COMIRESTROKE - ICF group will be compared against the rest of the participants. For hypothesis III, the COMIRESTROKE - NEFI group will be compared against the rest of the participants. A one-sided alternative will be tested according to our hypotheses. We will also implement the one-way ANOVA test to jointly compare all three groups for pre-post differences. In addition, a Tukey post-hoc comparison will be made to detect any further group differences beyond our hypotheses.

To assess the overall impact of rehabilitation and to compare effectiveness of different therapeutic approaches for Hypotheses I – III in more complex way, and to test for effect of other covariates in Hypothesis IV, a linear mixed effect model will be used with random patient effect fitted to longitudinal patient data. Measurement effect, group effect and their interaction, as well as effects of other covariates such as the level of disability in admission time will be tested by F test.

To address Goal I, correlations between changes in different examination scores will be evaluated using Pearson correlation coefficient and its nonparametric analogies. A cluster analysis will be performed to identify different phenotypes. This will allow the identification of different groups of patients in relation to the efficacy of the neuro-rehabilitation programs.

To address Goal II, for selected multi-item instruments, item-response theory (IRT) and generalized linear regression models will be used to study differential item functioning with respect to rehabilitation groups. Account will be taken for other respondent characteristics. Use will be made of differential item functioning in change (DIF-C) analysis (7) in order to detect between-group differences.

2.10. Statistical software

Analysis will be performed using the free statistical environment R (98) and its libraries. The lme (99) and nlme (100) library will be used for implementing mixed effect models. Library difNLR (101) will be used for the detection of DIF. Modules of the interactive ShinyItemAnalysis application will enable lme (99), nlme (100) and difNLR (101) library sample analyses to be interactively displayed (102).

3. Discussion

Undoubtedly, early intensive and complex rehabilitation is necessary for people after ischemic stroke (103). To address all functions and activities of the patient, the ICF model (3) provides systematic categorization potentially increasing the effectiveness of therapy (104). This clinical trial will implement a biopsychosocial approach in which individual goals set by an interdisciplinary team and rehabilitator will take into account the functioning, activity and participation level of the patient. To date, no study implementing the ICF model, has evaluated the effectiveness of rehabilitation in comparison with other interventions. (14, 105).

Ischemic stroke causes an extensive range of clinical dysfunctions. To narrow the program, motor disability was chosen as one of the inclusion criteria, as it is the most common and widely recognised problem (8). Motor recovery provides a direct means of addressing the effectiveness of therapy. Nineteen intervention types relevant to motor recovery after stroke have been identified (8). The most commonly applied include those involving Motor/Skill acquisition and Technology-based individualized interventions where the patient is increasingly active in the motor re-training process and the principles of sensory-motor learning are applied. Neurophysiological approaches including Bobath which stimulate neuroproprioceptive "facilitation, inhibition" (106, 107), are rarely utilised. In the Czech Republic, Vojta reflex locomotion, is routinely used in clinical practice. To date, only one very recent study has documented its effectiveness in stroke patients (108). This clinical trial should confirm this promising finding, and moreover enable the comparison of its effectiveness with alternative rehabilitation approaches implementing technology-based physiotherapy as well as those applying the ICF model. Importantly, this clinical trial will enable the systematic collection of demographics, biometric and molecular marker information allowing an opportunity for association analysis that may provide further evidence identifying indicators of effective rehabilitation. It is expected that the treatment will be much more effective in patients who start the rehabilitation soon after the ischemic stroke event. Patients will be scored for disability, personality traits, cardiovascular function and cognitive ability as outlined above.

Information gathered regarding whether a person will benefit from rehabilitation at a particular time point will improve the management of care in post-stroke people (17). Significant regard will be given to a participants' subjective feelings about how they feel they have improved, with tests chosen that provide a psychometric basis of assessment (109-111). If a correlation is confirmed between such tests and specific treatment, it will increase the likelihood of implementation into clinical stroke practice as quality indicators (72). Secondary outcomes have been chosen mainly in accordance with the Cranio-program (112). While financially demanding, the general health insurance system of the Czech Republic, requires fulfilment of a number of the above-standard conditions (for example, comprehensive testing - see table 2; and minimally 4 hours of rehabilitation per day). Recommended tests have been supplemented by objective examinations which may provide more extensive information e.g., Nine Hole Peg Test or the Hand Dynamometer. Moreover, specialized technological methods for assessing tremor (78) and dysarthria (87) have been supplemented with the aim of comprehensively describing algorithms of tremor and speech in people after stroke. To avoid overburdening patients, the examination will be effectively organized over two days. Additionally, examination by a clinical psychologist and speech therapist will be done in such a way as to

bring a therapeutic effect. One of the most important outputs of this clinical trial will be the recommendation concerning which clinical tests and scales are the most useful in post-stroke rehabilitation based on the framework of the ICF model. As in clinical practice, outcome measurements are used to guide rehabilitation programs, we consider that an item-level analysis may provide a deeper insight into the effectiveness of different interventions.

The benefits of previous rehabilitation have already been confirmed in individuals in the late phase after stroke (4, 113). In the context of the ICF model, it is important to assess the impact of rehabilitation from a long-term perspective (114). This clinical trial will document the enduring effect of rehabilitation after the subacute phase. This is the most important phase for recovery involving spontaneous improvement as well as benefits arising from previous therapeutic intervention (10).

In future, rehabilitation strategies should consider molecular biomarkers as indicators of improvements in neurobiological principles that support repair or compensatory strategies that stimulate adaptive responses in people after stroke (115). The role of lncRNA e.g., *MALAT1, SNHG12, MEG3* and *H19*, in ameliorating IS brain injury has now been recognised (25). They are pivotal factors in neuronal repair processes and enhance neurogenesis. Nevertheless, there is a lack of human studies and clinical trials involving lncRNAs in IS treatment. The medical community has stressed the urgency of implementing studies that may clarify the clinical impact of lncRNAs in the specific context of IS given their promising involvement in nervous system recovery.

In conclusion, the proposed clinical trial will determine the effectiveness of various rehabilitation approaches via analysis of physical, emotional and biological readouts. Therefore, this clinical trial will offer an innovative approach and will provide new direct and biological evidence of the effect of implementing the ICF model into the rehabilitation therapeutic arena.

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Informed consent form

Patient name:

Birthdate:

The patient was included in the study under the number:

Name of the authorized expert for this study:

1. I, the undersigned, agree to my participation in the study. I am over 18 years old.

2. I have been informed in detail about the objectives of the study, its procedures, and what is expected of me. The doctor in charge of the study explained to me the expected benefits and possible health risks that might arise during my participation in the study and explained how it would proceed if it occurred in an adverse event. I acknowledge that the study being conducted is a research activity. If the study is randomized, the probability of randomization to different treatment groups is taken into account.

3. I have informed the doctor in charge of all the medicines I have taken in the last 28 days, including those I am currently taking. If a medicine is prescribed to me by another doctor, I will inform him of my participation in the clinical study and I will not take it without the consent of the doctor in charge of that study.

4. I will work with my doctor during my treatment and will inform him immediately if any unusual or unexpected symptoms occur.

5. I will not be a blood donor for the duration of the study and for another 4 weeks after its completion.

6. I understand that I may suspend or withdraw from my participation at any time without affecting the course of my further treatment. My participation in the study is voluntary.

7. When enrolled in the study, my personal data will be kept with full protection of confidentiality according to the valid laws of the Czech Republic. Based on my consent, they will be able to inspect my original medical records in order to verify the data obtained by representatives of independent ethics committees and foreign or local competent authorities. For these cases, the confidentiality of my personal data is guaranteed. In the actual conduct of the study, personal data may be provided to entities other than those mentioned above only without identification data, ie anonymous data under a numerical code. Also for research and scientific purposes, my personal data can only be provided without identification data (anonymous data) or with my express consent.

8. There is no reward for my participation in the study.

9. I understand that my name will never appear in papers on this study. I agree with the use of the results from this study.

10. I have received a signed copy of this informed consent.

Patient's signature:

Signature of the specialist in charge of this study:

Date: