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# Intermittent Theta Burst Stimulation applied during early rehabilitation after stroke: Study protocol for a randomized controlled trial

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## Abstract

**Introduction:** Intermittent theta burst stimulation (iTBS) applied to primary motor cortex (M1) has been shown to modulate both the excitability and connectivity of the motor system. A recent proof-of-principle study, based on a small group of hospitalized stroke patients due to acute cerebral ischemia, suggested that adding iTBS (applied over the ipsilesional M1) to physiotherapy early after stroke for five consecutive days can amplify motor recovery with lasting after-effects. A randomized controlled clinical trial using a double-blind design is warranted to justify the implementation of iTBS-assisted motor rehabilitation in the neurorehabilitation from an acute ischemic stroke.

**Methods/design:** We investigate the effects of daily iTBS on early motor rehabilitation after stroke in an investigator-initiated, longitudinal randomized controlled trial. Patients (n=150) with hemiparesis receive iTBS (600 pulses) applied to the ipsilesional motor cortex (M1) or a control site (i.e., the parieto-occipital vertex). On eight consecutive workdays, a 45 min arm-centered motor training follows the intervention. The relative grip strength defined as the grip force ratios of the affected and unaffected hand serves as the primary outcome parameter. Secondary outcome parameters are measures of arm function (Action Research Arm Test, Fugl-Meyer Motor Scale), stroke severity (National Institutes of Health stroke scale), stroke-induced disability (modified Rankin Scale, Barthel Index), duration of inpatient rehabilitation, quality of life (EuroQol 5D), motor evoked potentials (MEP), and the resting motor threshold (RMT) of the ipsilesional M1.

**Discussion:** The results of this trial will clarify whether combining iTBS with physiotherapy early after stroke amplifies motor recovery in a clinical setting. The sample size enables subgroup analyses aiming at identifying response predictors.

**Ethics and dissemination:** The local ethics board provided ethics approval. We will submit the results of the study for publication in a peer-reviewed journal regardless of whether the results are positive, negative, or inconclusive.

**Keywords:** rehabilitation, hemiparesis, iTBS, TMS, motor recovery

## Article Summary

*Strengths and limitations of this study*

- The present study is a randomized, controlled, double-blind, single-center trial assessing the efficacy of iTBS in patients with acute cerebral ischemia.
- Interventions are applied before daily physiotherapy in the first few days after stroke since previous work suggests higher neural plasticity during the acute, compared to the chronic phase.
- Patients receive iTBS during their hospitalization warranting the adequate assessment of adverse events.
- A limitation of the study is a potential selection bias, given the patients' expected comorbidities, which may pose a risk for the application of repetitive transcranial magnetic stimulation or compromise the ability to provide informed consent.

## Introduction

Stroke is one of the leading causes of acquired long-term disability in adults worldwide. From 1990 to 2010, the prevalence of stroke has reached numbers of 500-1000 per 100 000 people in North America and European countries [1]. Although recent developments in the acute treatment of a stroke such as, e.g., thrombolysis or thrombectomy, effectively reduce both morbidity and mortality after a stroke [2], the majority of patients is still left with permanent motor deficits. More than 50 % of stroke survivors develop a persisting impairment, affecting the patients' activities of daily living [3,4].

Functional recovery has been shown to arise, at least in part, from the reorganization of functional brain networks, with intact neural structures compensating the loss of specialized neural circuitry damaged by the lesion [5,6]. Importantly, a focal brain lesion as induced by a stroke also interferes with the neural processing in distant brain regions, thereby affecting the brain at a network level. In this context, neuroimaging studies have frequently reported altered brain activity in motor-related cortical areas of both hemispheres, even for lesions affecting primarily deep white matter [7-9]. Longitudinal data revealed that in the first days after stroke, the activity of primary motor cortex is typically decreased, particularly in patients with severe motor deficits despite structurally intact motor cortex [8]. This pattern is typically followed by a bihemispheric increase of activity, which correlates with the amount of early motor recovery. However, best predictors for functional motor recovery are high levels of activity in the ipsilesional motor cortex as well as an activity pattern lateralized to the ipsilesional hemisphere [10,11]. Thus, restoring neural activation, particularly in the lesioned hemisphere, seems to be essential for functional recovery after stroke.

Comparable effects have been found for changes of motor-cortical excitability as probed by transcranial magnetic stimulation (TMS) [12]. In parallel to the initial decrease of neural activation observed in the ipsilesional M1 [8], TMS studies have also found lower excitability of this region, which correlated with the severity and prognosis of motor deficits [13,14].

To date, first-line rehabilitative strategies of improving motor deficits are based on functional training, i.e., physical or occupational therapy early after stroke [15,16]. Such behavioral interventions have been demonstrated to facilitate neural reorganization [17]. Accumulating evidence suggests that non-invasive brain stimulation techniques such as repetitive TMS (rTMS) may enhance neuroplasticity, thereby facilitating neural reorganization and recovery from stroke deficits [18,19]. Particularly the observation of decreased ipsilesional excitability early after stroke has led to the hypothesis that rTMS may be capable of increasing excitability and thus aiding functional recovery [20]. This effect has been demonstrated for different rTMS protocols varying in stimulation frequency, pattern, and the number of pulses [21,22]. Of note, rTMS may not only aid neural reorganization within the stimulated region but also modulates the activity of interconnected brain regions, e.g., the dorsal premotor cortex or the supplementary motor area, as shown for both healthy subjects [23] and stroke patients [24]. Thus, rTMS applied to M1 likely results in a system-wide change of neural activity in both hemispheres. At the behavioral level, proof-of-principle studies indicate that a single session of rTMS applied to ipsilesional M1 may transiently improve motor function of the paretic hand [25,26]. Further, a critical factor for a therapeutic effect seems to be the combination of plasticity-enhancing interventions with motor training, possibly leading to a better consolidation of (re-)learned motor skills [27-29].

While several rTMS studies in stroke patients reported transient improvements in motor function, other studies failed to demonstrate lasting beneficial effects [30-33]. For example, a recently published randomized controlled trial (RCT) with a large sample size (n=167) failed to demonstrate a beneficial effect of contralesional 1 Hz stimulation paired with arm motor training in chronic stroke patients, despite promising data from a relatively large number of pilot studies with small sample sizes (usually 10-20 patients). One likely reason may be the time window of intervention, which, in most studies, targeted the chronic phase after stroke.

Substantial functional recovery alongside high levels of neural plasticity is observed in the acute and subacute phase after stroke [34]. In contrast, the effectiveness of behavioral

interventions gets more and more limited the more time elapsed since the onset of the stroke. This negative effect may also be true for rTMS-mediated excitatory effects and its potential to support the recovery of function and neurorehabilitation. It thus seems reasonable to also conduct rehabilitative rTMS interventions in the acute and subacute phase after stroke [5]. Indeed, recent evidence from our group has indicated lasting beneficial effects of rTMS on motor recovery in a sample of stroke patients in the first few days after stroke [24]. In this study, two groups of early subacute stroke patients (each n=13, on average seven days post-stroke) received intermittent theta burst stimulation (iTBS, 600 pulses, 70 % RMT) for five days either covering ipsilesional M1 or a control site over the parieto-occipital vertex. Recovery of grip strength as measured by the relative grip strength was stronger in the M1-stimulated group than in the control-stimulated group, with the beneficial effect persisting at least three to six months. Of note, the small sample size of the follow-up groups and the heterogeneity of post-interventional treatments across patients preclude a reliable estimation of the clinical utility of combined iTBS and physiotherapy in (sub-)acute stroke patients to date. While studies with similarly small sample sizes corroborate a positive effect of M1-modulation by non-invasive brain stimulation after stroke [31], large RCTs are widely lacking.

**Aims and hypotheses**

Accordingly, this study aims to investigate the efficacy of combining iTBS over the ipsilesional M1 (real) versus iTBS over a parieto-occipital control site, priming physiotherapy in the early rehabilitation of stroke patients suffering from impaired hand motor function. Thereby, the main goal of our study is to demonstrate the effectiveness of iTBS in supporting the recovery of motor function in a sufficiently powered sample, expecting stronger rehabilitation effects on relative grip strength (primary outcome parameter) in the M1-iTBS group compared to the control-stimulation treated group. Furthermore, by assessing secondary outcome parameters (ARAT, Fugl-Meyer assessment), we also test whether combining iTBS with physiotherapy during early rehabilitation may influence more complex motor functions of the impaired upper extremity. We hypothesize that the combination of physical training with iTBS over ipsilesional

M1 significantly enhances motor recovery after stroke compared to physical training combined with control stimulation.

## Methods

### *Study design, recruitment, and procedure*

This randomized, controlled, double-blind, single-center trial is conducted at the Department of Neurology University Hospital Cologne, Germany. Hospitalized early subacute stroke patients (within the first 14 days post-stroke), suffering from a hand motor deficit due to ischemic stroke, are screened for study participation by a stroke-specialized neurologist. Eligible patients are invited to participate in the study by the investigator, who obtains written informed consent. Several motor scores, as well as the general neurological status and electrophysiological measures of motor-cortical excitability, are assessed at the day of enrolment (T0) as well as one day after the last iTBS intervention (T9). A longitudinal follow-up after three to six months (T10) assesses after-effects that extend into the chronic post-stroke phase. Of note, the first post-intervention assessment at T9 takes place one day after stimulation and hence does not reflect immediate stimulation after-effects. All patients undergo the same experimental procedure receiving iTBS interventions before physiotherapy on days T1-T8 (Fig. 1), the latter conducted as a routine part of the early rehabilitation program provided by the Department of Neurology, University Hospital Cologne. This program (total duration of 300 min per day) includes daily physiotherapy, occupational, and speech therapy, for at least two weeks. This time frame determines the duration of the iTBS intervention phase, which aims at eight stimulations on consecutive workdays. Note that the intended stimulation period is more extended than the five stimulations employed in our pilot study [24] in order to increase the total stimulation dose. In case that 8 stimulations cannot be performed due to organizational reasons (e.g., transfer of the patient to another rehab center), a minimum of five stimulations is necessary to be included into the final analysis [24]. A stimulation period longer

than 8 days was not considered feasible without delaying further medical plans or subsequent treatment after transfer to a rehabilitation center. Importantly, both groups receive the same amount of motor training, with cohorts solely differing in receiving M1-iTBS or control-iTBS before the physiotherapy session (for details on the trial, as standardized by the WHO, please see Tab. 1).

*Patient and public Involvement*

The study was designed based on the available literature related to optimizing motor recovery of stroke patients using iTBS, as described in the introduction. There was no patient of public involved in designing the study. The study protocol was written using the SPIRIT guidelines [35] to enhance the quality and transparency of the trial.

*iTBS protocol*

As a predominantly facilitatory rTMS protocol, iTBS has been rendered safe and effective, increasing cortical excitability in healthy subjects [36] and acute stroke patients [37]. One session of iTBS consists of 3 pulses delivered at a frequency of 50 Hz every 200 ms during 2 s (10 bursts), which are repeated every 10 s for a total duration of 3.5 min (600 pulses) [36]. Compared to other facilitatory rTMS protocols, the short duration of the intervention (3.5 min) enables a good integration of iTBS in training schedules even when patients are severely affected. The second advantage of iTBS is its relatively low stimulation intensity, reducing the risk of adverse reactions, particularly seizures [38]. The stimulation intensity of iTBS is individually adapted in each patient according to the excitability of the ipsilesional motor cortex. The original iTBS protocol, as published by Huang and colleagues [36], set the stimulation intensity to 80 % of the active motor threshold (AMT). However, assessment of the AMT requires subjects to perform constant contractions of the hand muscles, which is often

impossible for stroke patients with severe hand motor weakness. The present study, therefore, set stimulation intensities to 70 % of the RMT, which is independent of the patients' motor abilities. Of note, using 70 % RMT instead of 80 % AMT has been repeatedly demonstrated to induce comparable aftereffects on cortical excitability [23,39,40], allowing an effective application of iTBS in stroke [24].

*Inclusion- and exclusion criteria*

Inclusion and exclusion criteria are defined in line with previous iTBS studies in stroke [23,24] and the guidelines for the use of rTMS in clinical practice and research [38,41,42].

Inclusion criteria are:

- Written informed consent
- Age 40-90 years
- Ischemic stroke
- Hemiparesis with impaired unilateral hand motor function

Exclusion criteria are:

- Subjects legally detained in an official institute
- Participation in a clinical trial within the last 12 weeks
- Electronic or ferromagnetic implants located in the head, neck or thorax (e.g., clips, intracranial shunt, artificial heart valve, pacemaker, medication pump)
- Metal splinters in eye or head
- Pregnancy/breastfeeding
- Severe neurodegenerative disease (e.g., Parkinson's disease, Alzheimer's disease)
- Severe neuroinflammatory disease (e.g., multiple sclerosis)
- History of seizures/epilepsy
- Physical addiction to alcohol, medication, or drugs (excluded: nicotine)
- Insufficient compliance

- Present or past malignant tumor involving the central nervous system
- Severe psychiatric disease (e.g., schizophrenia)
- Bilateral hemiparesis or infarcts to the primary motor cortex or the corticospinal tract in the hemisphere ipsilateral to the hemiparesis
- Pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions affecting the primary motor cortex or the corticospinal tract, excluding minor small vessel disease changes (e.g., clinically asymptomatic lacunae <1cm)
- Known brain lesion (surgical, traumatic)
- Evidence for enhanced cerebral pressure
- Severe cardiac dysfunction
- Life expectancy < 12 months
- NIHSS Score at enrolment > 20
- Blood glucose imbalances resistant to treatment (<50 mg/dl or >300 mg/dl)
- Elevated blood pressure resistant to treatment (RR > 185/110mmHg)
- Systemic thrombolysis using r-tPA or thrombectomy within the last 24 hours before enrolment in the study
- Medication with benzodiazepines, high-potency antipsychotics, or tricyclic antidepressants before hospitalization or long-term during hospitalization

*Outcome measures*

The primary endpoint of this study is relative grip strength defined as of the maximum grip strength of the affected (paretic) hand compared to the unaffected hand, assessed three to six months after the intervention, i.e., in the chronic phase post-stroke. A stroke leading to hemiparesis typically reduces grip strength. In turn, recovery of grip strength usually precedes the recovery of other motor domains such as dexterity or movement speed [43]. Furthermore, grip strength seems to be mediated by contralateral M1 activity [44]. Therefore, stimulation of this region by iTBS may facilitate the recovery of grip strength during early rehabilitation [24].

Secondary endpoints comprise different measures of gross and fine upper limb function assessed by the Action Research Arm Test (ARAT [45]) and the Fugl-Meyer Motor Scale (FM [46]) of the upper extremity, stroke severity measured by the National Institutes of Health stroke scale (NIHSS), general disability (modified Rankin Scale, mRS [47]), and quality of life (EuroQol 5D including the visual analogue scale, EQ-5D). Moreover, in order to obtain electrophysiological measures of corticospinal integrity, motor evoked potentials (MEP) and the RMT of the ipsilesional M1 are included as secondary endpoints. Finally, to account for differences in rehabilitation treatments between completion of the intervention (T9) and the follow-up assessment (T10), we document the performance in activities of daily living assessed by the Barthel scale as well as the duration of stay in external rehabilitation facilities.

In sum, these tests provide a detailed assessment, monitoring the clinical and electrophysiological condition of patients before and after iTBS (Tab. 2).

*Randomization and stratification*

After obtaining informed consent, randomization is performed using the 24/7 online randomization tool ALEA (FormsVision BV, Abcoude, NL). Patients are allocated 1:1 into the intervention groups, receiving “verum” or “control” iTBS. In order to balance groups regarding potential confounding factors, randomization is stratified based on patients’ age (≤ 68, >68 years), motor impairment (relative grip strength < 10 %, 10 – 70 %, > 70 %), and stimulation intensity (≤ 50 %, > 50 % maximal stimulator output), as these factors are known to impact on motor recovery post-stroke [48,49].

*Statistical analysis*

After data collection, confirmatory and descriptive analyses will be conducted. In our proof-of-principle study, we obtained data from a smaller sample [22], which revealed three to six

months after the intervention an increase of grip strength of 38.1 ± 28.7 % in patients treated by iTBS versus 26.2 ± 11.7 % in the control stimulation group. Thus, the observed effect strength amounted to 0.54. Using an unpaired t-Test with a two-sided 5 % type I error and a power of 80 %, a sample of 110 patients is required (calculated using the software G*Power 3.1.7). Assuming a drop-out rate of 25 % based on the cohort of Volz and colleagues (2016), an estimated sample of 150 recruited patients is needed.

Variables are analyzed descriptively using mean, standard deviations, quantiles (0, 25, 50, 75, 100), or count and frequency, respectively. The final statistical analysis is carried out in an intention to treat (ITT) collective including all patients who received at least one intervention (verum or control) with a subsequent grip strength testing, to assess the safety and efficacy of iTBS. Moreover, a supportive analysis is performed based on the “per protocol” (PP) collective, which includes all patients who underwent at least five [24] interventions (verum or control) and provided grip force measures at baseline and the three to six months follow-up.

The primary endpoint, i.e., the change in grip strength after three months (T10), is analyzed using a linear mixed model with repeated measurements, in which the factors group (verum, control), time, group x time, and strata at baseline (age, motor impairment, stimulation intensity) will be entered. Moreover, the model will account for the number of data points obtained during the intervention phase (T1 – T9). The primary hypothesis is addressed using a customized test (contrast) to compare the change from baseline (T0) to three to six months (T10) between the two treatment groups. Mean difference, corresponding 95 % confidence interval, and the p-value (two-sided) will be presented.

All secondary variables will be analyzed similarly or using unpaired t-tests or Mann-Whitney U tests, respectively. (Serious) Adverse events are listed. Subgroup analyses will be performed for randomization stratification variables and length of rehabilitation therapy. The current version of SPSS Statistics (IBM Corp., Armonk, NY, USA) will be used for the statistical analyses.

*Blinding*

The study is carried out using a double-blinded design, in which neither the patients nor the testing physicians or statisticians are aware of the intervention arm (verum or control). As applying iTBS over different stimulation sites (depending on the patients' intervention arm) implicates that physicians performing the intervention cannot be blinded, the intervention team needs to be separated into blinded physicians performing patient recruitment and examinations, and unblinded physicians exclusively applying iTBS. Thereby, we ensure that both patients and investigators are blinded during the assessment of outcome parameters throughout the entire study procedure. In the case of an emergency unblinding, investigators at the Department of Neurology have access to sealed envelopes labelled with the patients' randomization numbers. To maintain the quality of the trial, a patient's allocation should only be unblinded in exceptional circumstances when knowledge of the actual treatment is essential for the management of the patient.

*Safety*

The exclusion criteria of the present trial follow the latest safety recommendations for rTMS [38,42], thereby reducing the risk of adverse events or reactions to iTBS to a minimum. Adverse events (AE) or serious adverse events (SAEs) are assessed throughout the entire observation period of the study, including all scheduled visits T0 – T10. All events are reported to the federal authorities (Federal Institute for Drugs and Medical Devices, BfArM). In our pilot study [24], no severe adverse event occurred, especially no focal or generalized seizures.

*Documentation and quality assurance*

All data assessed during the trial are documented promptly after data acquisition and entered into the electronic case report form (eCRF) by the responsible investigators. Regular monitor

inspections ensure high quality of documentation and the correct implementation of the study protocol. The Clinical Trials Centre Cologne (CTCC Cologne) is responsible for the monitoring. Besides the initiation visit at the beginning and the close-out visit at the end of the study, monitoring visits are performed on average after every tenth patient included. Thus, at least 15 visits are scheduled. Monitoring visits include a review of source data documented in the eCRF, written consent, inclusion and exclusion criteria.

*Data collection and management*

CTCC Cologne performs the data management. The commercial online software TrialMaster™ (OmniComm.com) is used as a data management system, ensuring data safety by a firewall and backup system, including multiple data storage sites. The database was developed and validated by the CTCC Cologne.

All data collectors are stroke-specialized neurologists who have been trained in good clinical practice (GCP). After the investigators enter the data into the eCRF, the CTCC Cologne reviews the data for completeness and plausibility. The data manager and investigators resolve discrepancies and implausible entries.

Only researchers involved in the data collection, management and data analysis will have access to the final dataset. However, the principal investigator allows direct access to all source data and documents at monitoring, and inspection from federal authorities (Federal Institute for Drugs and Medical Devices, BfArM).

## Discussion

This prospective, randomized, controlled, double-blind clinical trial investigates the effects of combining iTBS with physiotherapy during the early rehabilitation phase on hand motor

recovery after a stroke-induced motor impairment. While training-based approaches including physical therapy and occupational therapy constitute the standard of rehabilitation treatment [15,50], the present study tests in a relatively large sample of stroke patients whether priming motor training by non-invasive plasticity-induction in ipsilesional M1 immediately before the training session may amplify motor recovery.

Previous studies, often conducted in the chronic phase after stroke, showed that both facilitatory rTMS over ipsilesional M1 and inhibitory rTMS over contralesional M1 can result in improved motor performance of the stroke-affected hand. However, daily interventions using rTMS in chronic stroke patients before motor training have led to inconsistent findings [19,51,52]. The first large sample (n=167) trial (NICHE trial) recently revealed that application of inhibitory rTMS over contralesional M1 in chronic stroke patients did not facilitate motor recovery compared to control stimulation [53]. Of note, the highest levels of neural plasticity have been found in the first few days and weeks after stroke [34]. Thus, the amplification of neuroplasticity using rTMS may be most effective during the acute and early subacute phase after a stroke. While data on neuromodulatory effects within the first few days and weeks after stroke remain scarce, recent findings suggest that increasing excitability of ipsilesional M1 using rTMS early after stroke may induce lasting beneficial effects on motor performance [24]. These findings support the hypothesis that rTMS may be applied in addition to physiotherapy to induce plasticity in the ipsilesional M1 and thereby promote motor outcome. As shown by fMRI before and after the rTMS intervention, patients in the verum rTMS group showed increased functional connectivity between the modulated stimulation site and a functionally related motor network including the dorsal premotor cortex and the supplementary motor area, compared with patients in the control stimulation group [24]. Given that without rTMS intervention patients during the first few days after stroke feature a loss of activity and connectivity in the ipsilesional hemisphere [54,55], the finding of increased connectivity with the verum stimulation site suggests that the beneficial effects of rTMS may not only result from inducing plasticity locally in M1, but also from enhancing connectivity with a functionally related motor network.

It is important to note that the data mentioned above rely on samples rarely exceeding n=15 patients per intervention arm. Since stroke patients are highly heterogeneous due to the interindividual variability of lesion location and size, neurological impairment, age, and medication, trials with larger samples are needed to systematically assess the impact of rTMS in the rehabilitation after stroke [19]. As mentioned above, the first large sample (n=167) trial (NICHE trial) recently revealed that application of inhibitory rTMS over contralesional M1 in *chronic* stroke patients did not facilitate motor recovery compared to control stimulation [53]. The present study is the first study with a large sample of *subacute* stroke patients (n=150), systematically assessing clinical deficits, structural images, comorbidity, and medication. Besides the sample size, a significant strength of the current study is its comprehensive monitoring of clinical and electrophysiological data, comprising clinical examinations and standardized scores before, during, and at least three months after the application of iTBS. Importantly, this randomized controlled trial is equipped with sufficient power to reveal either an effect of iTBS or an equally meaningful null result.

The stratification of age, motor deficit, and stimulation intensity further allows dissociating intervention effects in different subgroups. Considering the factors mentioned above of each patient is a critical step for implementing non-invasive brain stimulation in individualized rehabilitation programs in the future [56]. Similar to other rTMS studies in stroke patients, the present trial features the limitation of a potential selection bias, given the patients' expected comorbidities: Stroke is associated with comorbidities posing a risk for the application rTMS (i.e., structural epilepsy, cardiac pacemakers) and conditions compromising the ability to provide informed consent (i.e., aphasia, diminished level of consciousness) [57,58].

In summary, this study is the first randomized controlled trial probing the efficacy of iTBS on the primary motor cortex during motor rehabilitation in the first few weeks after stroke. The trial is sufficiently powered to detect positive or negative effects and to account for confounding factors. Together with other recently started large-scale RCTs on tDCS and rTMS in the contralesional hemisphere (www.clinicaltrials.gov), the findings of this trial will hopefully

improve our understanding of how to translate non-invasive brain stimulation into clinical practice, thereby improving rehabilitation for stroke patients.

## Trial status

At the time of submission, recruitment has not been completed.

## Abbreviations

AE: adverse event, AMT: active motor threshold, ARAT: Action Research Arm Test, CTCC: Clinical Trials Center Cologne, eCRF: electronic case report form; rTMS: repetitive Transcranial magnetic stimulation; EV: Evaluation visit, FM: Fugl-Meyer Motor Scale of the upper extremity, GCP: good clinical practice, iTBS: intermittent theta-burst stimulation, M1: primary motor cortex, MEP: motor evoked potential, mRS: modified Rankin Scale, NIHSS: National Institutes of Health stroke scale, tDCS: transcranial direct current stimulation, RCT: randomized controlled trial, RMT: resting motor threshold, r-tPA: recombinant tissue-type plasminogen activator, SAE: serious adverse event



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## Author contributions

CG, LH, LJV, and GRF developed the study design and wrote the statistical analysis plan in collaboration with DK and SH. LH, CR, CG, and GRF perform the clinical evaluation. CT conducts rTMS interventions. LH and CG wrote the first draft of the manuscript. CT, LJV, and GRF revised it for intellectual content. All authors read and approved the final manuscript.

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## Competing interests

None of the authors have anything to disclose.

## Ethics approval and consent to participate

The ethics board of the University Hospital of Cologne (reference number 15 - 343) approved the study and its amendments:

First approval November 2nd 2015 (original version).

Amendment (version 2.22) approved and implemented December 20th 2016. Specification of exclusion criteria.

Amendment (version 3) approved and implemented November 15th 2018. Change of inclusion and exclusion criteria.

Written informed consent is obligatory before study participation. The study is registered at the German Clinical Trials Register (DRKS, www.drks.de, DRKS-ID: DRKS00008963) and the ClinicalTrials.gov database (Identifier: NCT02910024).

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**Table 1**

| Trial characteristics based on WHO trial registration dataset | |
|---|---|
| Data category | Trial information |
| Primary registry and trial identifying number | German Clinical Trials Register (DRKS)<br>DRKS-ID: DRKS00008963 |
| Date of registration in primary registry | 16 February 2016 |
| Secondary identifying numbers | ClinicalTrials.gov (NCT02910024) |
| Source(s) of monetary or material support | The study is conducted as an investigator initiated study supported by the Max-Delbrück Prize to GRF and by the University of Cologne Emerging Groups Initiative (CONNECT group; CG and GRF) implemented into the Institutional Strategy of the University of Cologne and the German Excellence Initiative. |
| Primary sponsor | University of Cologne, Albertus-Magnus-Platz 50923 Cologne |
| Secondary sponsor | NA |
| Contact for public queries | Prof. Dr. Gereon R. Fink (gereon.fink@uk-koeln.de) |
| Contact for scientific queries | Prof. Dr. Gereon R. Fink (gereon.fink@uk-koeln.de) |
| Public title | Theta-Burst-Stimulation in early Rehabilitation of Stroke |
| Scientific title | Theta-Burst-Stimulation in early Rehabilitation of Stroke |
| Country of recruitment | Germany |
| Healthy conditions(s) or problems studied | Stroke with hemiparesis including impaired hand motor function |
| Interventions | Active Comparator: Real-rTMS<br>Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex in the lesioned hemisphere using the intermittent theta-burst-stimulation protocol (iTBS; application of 3 pulses with a frequency of 50 Hz, in a theta-rhythm of 5 Hz for 2 seconds, repeated every 10 seconds, duration of one session: about 3,5 minutes) before physiotherapy for 8 days<br><br>Sham Comparator: Sham-rTMS<br>Repetitive transcranial magnetic stimulation (rTMS) in sham position (tilted coil over parieto-occipital vertex) before physiotherapy for 8 days |
| Key inclusion and exclusion criteria | Inclusion Criteria: written consent, age: 40-90 years, ischemic stroke, hemiparesis with impaired hand motor function<br>Exclusion Criteria: Subjects who are legally detained in an official institute (§20 MPG), participation in clinical trial within the last 12 weeks, electronic implants or ferromagnetic Implants located in the head, neck or thorax (e.g. clips, intracranial shunt, artificial heart valve, pacemaker), medication pump (e.g. insulin pump), metal splinters in eye or head, pregnancy / breastfeeding, severe neurodegenerative disease, severe neuro-inflammatory disease, history of seizures / epilepsy, physical addiction to alcohol, medication, or drugs (excluded: nicotine), insufficient compliance, present or past malignant tumor involving the central nervous system, severe psychiatric disease, clinically |

| | |
|---|---|
| | manifest bilateral hemiparesis or infarcts in the primary motor cortex or along the corticospinal tract in the hemisphere ipsilateral to the hemiparesis, pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions in the primary motor cortex or along the corticospinal tract, excluding microvascular changes (e.g. clinically asymptomatic lacunae <1cm), known brain lesion (surgical, traumatic), evidence for enhanced cerebral pressure, severe cardiac dysfunction, life expectancy < 12 months, NIHSS Score > 20, blood glucose imbalances resistant to treatment (<50 mg/dl or >300 mg/dl), elevated blood pressure resistant to treatment (RR > 185/110mmHg), systemic thrombolysis using rt-PA or thrombectomy within the last 24 hours before enrollment in study, medication with benzodiazepines, high-potency antipsychotics or tricyclic antidepressants before hospitalization or long-term during hospitalization |
| Study type | Interventional<br>Allocation: randomized intervention model.<br>Masking: double blind (subject, caregiver, investigator, outcomes assessor)<br>Assignment: parallel<br>Primary purpose: treatment |
| Date of first enrolment | April 2016 |
| Target sample size | 150 |
| Recruitment status | Recruiting |
| Primary outcome(s) | Relative grip force (time frame: three to six months after enrollment) |
| Key secondary outcomes | Relative grip force (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Action Research Arm Test (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Fugl-Meyer Motor Scale of the upper extremity (time frame: after 8 days of intervention, and three to six months after enrollment)<br>National Instituts of Health Stroke Scale (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Modified Rankin Scale (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Motor evoked potential induced by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Resting motor threshold as measured by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and three to six months after enrollment)<br>EuroQol 5D questionnaire (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Barthel-Index at admission and discharge in external rehabilitation facility (time frame: three to six months after enrollment)<br>Days of rehabilitation after intervention phase (time frame: three to six months after enrollment) |

**Table 2**

| Study period | Pre-enrollment | T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visits | | | | | | | | | | | | |
| Screening (in-/exclusion criteria) | X | | | | | | | | | | | |
| Written informed consent | | X | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | |
| Medical history | X | X | | | | | | | | | | |
| Neuroimaging (MRI/CT) | X | | | | | | | | | | | |
| TMS-intervention (M1 iTBS/control iTBS) | | | X | X | X | X | X | X | X | X | | |
| Physiotherapy | | | X | X | X | X | X | X | X | X | | |
| Assessment of adverse events | | X | X | X | X | X | X | X | X | X | X | X |
| Relative grip strength | X | X | X | X | X | X | X | X | X | X | X | X |
| Documentation of medication | | X | X | X | X | X | X | X | X | X | X | X |
| Neurological examination | X | X | | | | | | | | | X | X |
| Electrophysiological examination (RMT, MEPs) | | X | | | | | | | | | X | X |
| Upper limb motor function (ARAT, FM) | | X | | | | | | | | | X | X |
| Stroke severity (NIHSS) | | X | | | | | | | | | X | X |
| Disability (mRS) | | X | | | | | | | | | X | X |
| Quality of life (EQ-5D) | | X | | | | | | | | | X | X |
| Assessment of external rehabilitation time | | | | | | | | | | | | X |

RMT: resting motor threshold; MEPs: Motor evoked potentials; ARAT: Action Research Arm Test; FM: Fugl-Meyer Motor Scale of the upper extremity; NIHSS: National Institutes of Health stroke scale; mRS: modified Rankin Scale; EQ-5D: EuroQol 5D including the visual analogue scale

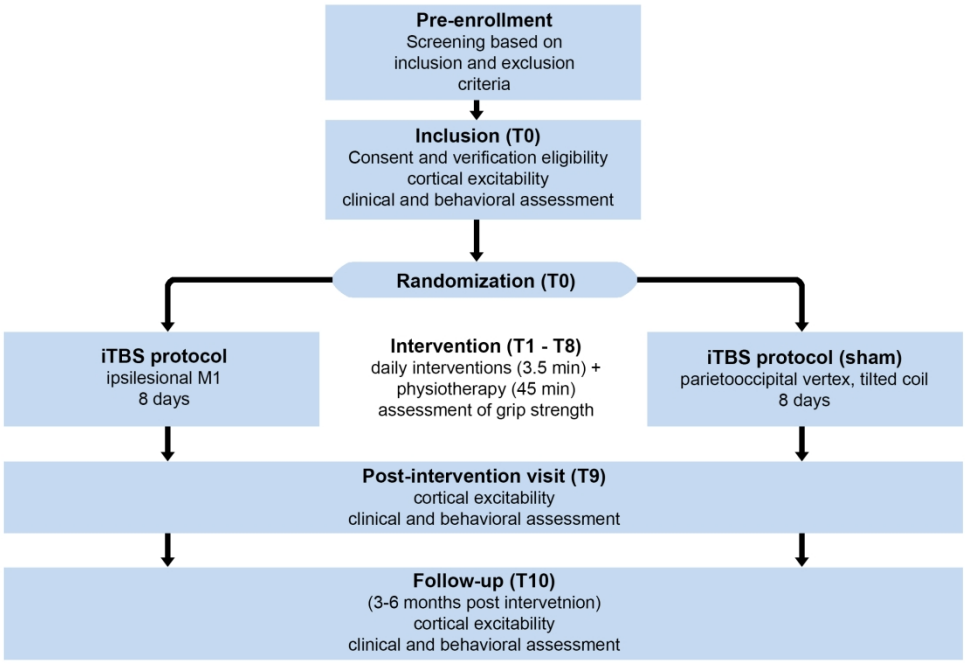


Figure 1. Flow chart of the study procedure

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 18 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 24-25 |
| Protocol version | #3 | Date and version identifier | 18 |
| Funding | #4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 17 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 18 |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-5 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 10 |
| Objectives | #7 | Specific objectives or hypotheses | 6-7 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 8-10 |

| | | | |
|---|---|---|---|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 8 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 13-14 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 10 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 26 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 11 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 11 |

| | | | |
|---|---|---|---|
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 14 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13-14 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11-12 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11-12 |

| | | | |
|---|---|---|---|
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 11-12 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 18 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 18 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13-14 |

| | | | |
|---|---|---|---|
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 14 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 2 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

BMJ Open

# Intermittent Theta Burst Stimulation applied during early rehabilitation after stroke: Study protocol for a randomized controlled trial



| | |
|---|---|
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# Intermittent Theta Burst Stimulation applied during early rehabilitation after stroke: Study protocol for a randomized controlled trial

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## Abstract

**Introduction:** Intermittent theta burst stimulation (iTBS) applied to primary motor cortex (M1) has been shown to modulate both the excitability and connectivity of the motor system. A recent proof-of-principle study, based on a small group of hospitalized stroke patients due to acute cerebral ischemia, suggested that adding iTBS (applied over the ipsilesional M1) to physiotherapy early after stroke for five consecutive days can amplify motor recovery with lasting after-effects. A randomized controlled clinical trial using a double-blind design is warranted to justify the implementation of iTBS-assisted motor rehabilitation in the neurorehabilitation from an acute ischemic stroke.

**Methods/design:** We investigate the effects of daily iTBS on early motor rehabilitation after stroke in an investigator-initiated, longitudinal randomized controlled trial. Patients (n=150) with hemiparesis receive iTBS (600 pulses) applied to the ipsilesional motor cortex (M1) or a control stimulation (i.e., coil placement over parieto-occipital vertex in parallel to the interhemispheric fissure and with a tilt of 45°). On eight consecutive workdays, a 45 min arm-centered motor training follows the intervention. The relative grip strength defined as the grip force ratios of the affected and unaffected hand serves as the primary outcome parameter. Secondary outcome parameters are measures of arm function (Action Research Arm Test, Fugl-Meyer Motor Scale), stroke severity (National Institutes of Health stroke scale), stroke-induced disability (modified Rankin Scale, Barthel Index), duration of inpatient rehabilitation, quality of life (EuroQol 5D), motor evoked potentials (MEP), and the resting motor threshold (RMT) of the ipsilesional M1.

**Ethics and dissemination:** The study was approved by the Ethics Commission of the Medical Faculty, University of Cologne, Germany (reference number 15-343). Data will be disseminated through peer-reviewed publications and presentations at conferences.


**Keywords:** rehabilitation, hemiparesis, iTBS, TMS, motor recovery

## Article Summary

*Strengths and limitations of this study*

- The present study is a randomized, controlled, double-blind, single-center trial assessing the efficacy of iTBS in patients with acute cerebral ischemia.
- Interventions are applied before daily physiotherapy in the first few days after stroke since previous work suggests higher neural plasticity during the acute, compared to the chronic phase.
- Patients receive iTBS during their hospitalization warranting the adequate assessment of adverse events.
- A limitation of the study is a potential selection bias, given the patients' expected comorbidities, which may pose a risk for the application of repetitive transcranial magnetic stimulation or compromise the ability to provide informed consent.

## Introduction

Stroke is a leading cause of acquired long-term disability in adults worldwide. From 1990 to 2010, the prevalence of stroke has reached numbers of 500-1000 per 100 000 people in North America and European countries [1]. Although recent developments in the acute treatment of a stroke such as, e.g., thrombolysis or thrombectomy, effectively reduce both morbidity and mortality after a stroke [2], the majority of patients is still left with permanent motor deficits. More than 50% of stroke survivors develop a persisting impairment, affecting the patients' activities of daily living [3,4].

Functional recovery has been shown to arise, at least in part, from the reorganization of functional brain networks, with intact neural structures compensating the loss of specialized neural circuitry damaged by the lesion [5,6]. Importantly, a focal brain lesion as induced by a stroke also interferes with the neural processing in distant brain regions, thereby affecting the brain at a network level. In this context, neuroimaging studies have frequently reported altered brain activity in motor-related cortical areas of both hemispheres, even for lesions affecting primarily deep white matter [7-9]. Longitudinal data revealed that in the first days after stroke, the activity of primary motor cortex is typically decreased, particularly in patients with severe motor deficits despite structurally intact motor cortex [8]. This pattern is typically followed by a bihemispheric increase of activity, which correlates with the amount of early motor recovery. However, best predictors for functional motor recovery are high levels of activity in the ipsilesional motor cortex as well as an activity pattern lateralized to the ipsilesional hemisphere [10,11]. Thus, restoring neural activation, particularly in the lesioned hemisphere, seems to be essential for functional recovery after stroke.

Comparable effects have been found for changes of motor-cortical excitability as probed by transcranial magnetic stimulation (TMS) [12]. In parallel to the initial decrease of neural activation observed in the ipsilesional M1 [8], TMS studies have also found lower excitability of this region, which correlated with the severity and prognosis of motor deficits [13,14].

To date, first-line rehabilitative strategies of improving motor deficits are based on functional training, i.e., physical or occupational therapy early after stroke [15,16]. Such behavioral interventions have been demonstrated to facilitate neural reorganization [17]. Accumulating evidence suggests that non-invasive brain stimulation techniques such as repetitive TMS (rTMS) may enhance neuroplasticity, thereby facilitating neural reorganization and recovery from stroke deficits [18,19]. Particularly the observation of decreased ipsilesional excitability early after stroke has led to the hypothesis that rTMS may be capable of increasing excitability and thus aiding functional recovery [20]. This effect has been demonstrated for different rTMS protocols varying in stimulation frequency, pattern, and the number of pulses [21,22]. Of note, rTMS may not only aid neural reorganization within the stimulated region but also modulates the activity of interconnected brain regions, e.g., the dorsal premotor cortex or the supplementary motor area, as shown for both healthy subjects [23] and stroke patients [24]. Thus, rTMS applied to M1 likely results in a system-wide change of neural activity in both hemispheres. At the behavioral level, proof-of-principle studies indicate that a single session of rTMS applied to ipsilesional M1 may transiently improve motor function of the paretic hand [25,26]. Further, a critical factor for a therapeutic effect seems to be the combination of plasticity-enhancing interventions with motor training, possibly leading to a better consolidation of (re-)learned motor skills [27-29].

While several rTMS studies in stroke patients reported transient improvements in motor function, other studies failed to demonstrate lasting beneficial effects [30-33]. A recently published large sample (n=167) trial (NICHE trial) revealed that application of inhibitory rTMS over contralesional M1 in chronic stroke patients failed to demonstrate a beneficial effect of contralesional 1 Hz stimulation paired with arm motor training in chronic stroke patients [34] despite promising data from a relatively large number of pilot studies with small sample sizes (usually 10-20 patients). One likely reason may be the time window of intervention, which, in most studies, targeted the chronic phase after stroke. Substantial functional recovery alongside high levels of neural plasticity is observed in the acute and subacute phase after stroke [35].

In contrast, the effectiveness of behavioral interventions gets more and more limited the more time elapsed since the onset of the stroke. This negative effect may also be true for rTMS-mediated excitatory effects and its potential to support the recovery of function and neurorehabilitation. Hence, the amplification of neuroplasticity using rTMS may be most effective during the acute and early subacute phase after a stroke. While data on neuromodulatory effects within the first few days and weeks after stroke remain scarce, recent evidence from our group has indicated lasting beneficial effects of rTMS on motor recovery in a sample of stroke patients in the first few days after stroke [24]. In this study, two groups of early subacute stroke patients (each n=13, on average seven days post-stroke) received intermittent theta burst stimulation (iTBS, 600 pulses, 70% RMT) for five days either covering ipsilesional M1 or a control with the TMS coil tilted over the parieto-occipital vertex. Recovery of grip strength as measured by the relative grip strength was stronger in the M1-stimulated group than in the control-stimulated group, with the beneficial effect persisting at least three to six months. As shown by fMRI before and after the rTMS intervention, patients in the verum rTMS group showed increased functional connectivity between the modulated stimulation site and a functionally related motor network, including the dorsal premotor cortex and the supplementary motor area, compared with patients in the control stimulation group [24]. Given that without rTMS intervention patients during the first few days after stroke feature a loss of activity and connectivity in the ipsilesional hemisphere [36,37,38], the finding of increased connectivity with the verum stimulation site suggests that the beneficial effects of rTMS may not only result from inducing plasticity locally in M1, but also from enhancing connectivity with a functionally related motor network. Taken together, these findings support the hypothesis that rTMS may be applied in addition to physiotherapy to induce plasticity in the ipsilesional M1 and thereby promote motor outcome. Of note, the small sample size of the follow-up groups and the heterogeneity of post-interventional treatments across patients preclude a reliable estimation of the clinical utility of combined iTBS and physiotherapy in (sub-)acute stroke patients to date. While studies with similarly small sample sizes corroborate a positive effect of M1-modulation by non-invasive brain stimulation after stroke [31], large RCTs are widely

lacking.

## Aims and hypotheses

Accordingly, this study aims to investigate the efficacy of combining iTBS over the ipsilesional M1 (real) versus iTBS over a parieto-occipital control site, priming physiotherapy in the early rehabilitation of stroke patients suffering from impaired hand motor function. Thereby, the main goal of our study is to demonstrate the effectiveness of iTBS in supporting the recovery of motor function in a sufficiently powered sample, expecting stronger rehabilitation effects on relative grip strength (primary outcome parameter) in the M1-iTBS group compared to the control-stimulation treated group. Furthermore, by assessing secondary outcome parameters (ARAT, Fugl-Meyer assessment), we also test whether combining iTBS with physiotherapy during early rehabilitation may influence more complex motor functions of the impaired upper extremity. This study will be the first with a large sample of early subacute stroke patients (n=150), systematically assessing clinical deficits, electrophysiological data, structural images, comorbidity, and medication before, during, and at least three months after the application of iTBS. We hypothesize that the combination of physical training with iTBS over ipsilesional M1 significantly enhances motor recovery after stroke compared to physical training combined with control stimulation.

## Methods

### *Study design, recruitment, and procedure*

This prospective, randomized, controlled, double-blind, single-center trial is conducted at the Department of Neurology University Hospital Cologne, Germany. Hospitalized early subacute stroke patients (within the first 14 days post-stroke), suffering from a hand motor deficit due to ischemic stroke, are screened for study participation by a stroke-specialized neurologist.

Eligible patients are invited to participate in the study by the investigator, who obtains written informed consent. Several motor scores, as well as the general neurological status and electrophysiological measures of motor-cortical excitability, are assessed at the day of enrolment (T0) as well as one day after the last iTBS intervention (T9). A longitudinal follow-up after three to six months (T10) assesses after-effects that extend into the chronic post-stroke phase. Of note, the first post-intervention assessment at T9 takes place one day after stimulation and hence does not reflect immediate stimulation after-effects. All patients undergo the same experimental procedure receiving iTBS interventions before physiotherapy on days T1-T8 (Figure 1), the latter conducted as a routine part of the early rehabilitation program provided by the Department of Neurology, University Hospital Cologne. This program (total duration of 300 min per day) includes daily physiotherapy, occupational, and speech therapy, for at least two weeks. This time frame determines the duration of the iTBS intervention phase, which aims at eight stimulations on consecutive workdays. Note that the intended stimulation period is more extended than the five stimulations employed in our pilot study [24] in order to increase the total stimulation dose. In case that 8 stimulations cannot be performed due to organizational reasons (e.g., transfer of the patient to another rehab center), a minimum of five stimulations is necessary to be included into the final analysis [24]. A stimulation period longer than 8 days was not considered feasible without delaying further medical plans or subsequent treatment after transfer to a rehabilitation center. Importantly, both groups receive the same amount of motor training, with cohorts solely differing in receiving M1-iTBS or control-iTBS before the physiotherapy session (see below). Details on trial characteristics, based on the WHO trial registration dataset are provided in Table 1.

*Patient and public involvement*

The study was designed based on the available literature related to optimizing motor recovery of stroke patients using iTBS, as described in the introduction. There was no public involvement in the study design.

*iTBS protocol*

As a predominantly facilitatory rTMS protocol, iTBS has been rendered safe and effective, increasing cortical excitability in healthy subjects [39] and acute stroke patients [40]. One session of iTBS consists of 3 pulses delivered at a frequency of 50 Hz every 200 ms during 2 s (10 bursts), which are repeated every 10 s for a total duration of 3.5 min (600 pulses) [39]. For patients assigned to the study arm receiving an effective intervention, the protocol is applied over the ipsilesional M1, whereas patients in the control group receive iTBS over the parieto-occipital vertex, corresponding to the POz location of a 10-20 EEG system. Importantly, to prevent effective stimulation of cortical tissue in the control condition, the handle of the coil was placed parallel to the interhemispheric fissure pointing to the front. Besides, the coil was tilted upwards about 45°, touching the skull not with the center but with the rim to increase the coil-brain distance. This procedure induces similar acoustic and tactile effects as M1 stimulation without leading to a change of motor behavior, motor cortical excitability, or neural activity as measured with fMRI [23,24,41,42,43]. Compared to other facilitatory rTMS protocols, the short duration of the intervention (3.5 min) enables a good integration of iTBS in training schedules even when patients are severely affected. The second advantage of iTBS is its relatively low stimulation intensity, reducing the risk of adverse reactions, particularly seizures [44]. The stimulation intensity of iTBS is individually adapted in each patient according to the excitability of the ipsilesional motor cortex. The original iTBS protocol, as published by Huang and colleagues [39], set the stimulation intensity to 80% of the active motor threshold (AMT). However, assessment of the AMT requires subjects to perform constant contractions of the hand muscles, which is often impossible for stroke patients with severe hand motor weakness. The present study, therefore, set stimulation intensities to 70% of the RMT, which is independent of the patients' motor abilities. Of note, using 70% RMT instead of 80% AMT has been repeatedly demonstrated to induce comparable aftereffects on cortical excitability [23,45,46], allowing an effective application of iTBS in stroke [24]. As shown in our proof-of-

principle study [24], stimulation thresholds may exceed the maximum stimulator output (MSO) in case of a severe disruption of the corticospinal tract leading to no recordable MEPs. Here, the stimulation intensity is set to 50% MSO, which represents the upper limit for 50-Hz stimulation using a standard Magstim SuperRapid2 stimulator and which has been proven to be safe.

*Inclusion- and exclusion criteria*

Inclusion and exclusion criteria are defined in line with previous iTBS studies in stroke [23,24] and the guidelines for the use of rTMS in clinical practice and research [44,47,48].

Inclusion criteria are:

- Written informed consent
- Age 40-90 years
- Ischemic stroke
- Hemiparesis with impaired unilateral hand motor function

Exclusion criteria are:

- Subjects legally detained in an official institute
- Participation in a clinical trial within the last 12 weeks
- Electronic or ferromagnetic implants located in the head, neck or thorax (e.g., clips, intracranial shunt, artificial heart valve, pacemaker, medication pump)
- Metal splinters in eye or head
- Pregnancy/breastfeeding
- Severe neurodegenerative disease (e.g., Parkinson's disease, Alzheimer's disease)
- Severe neuroinflammatory disease (e.g., multiple sclerosis)
- History of seizures/epilepsy
- Physical addiction to alcohol, medication, or drugs (excluded: nicotine)
- Insufficient compliance

- Present or past malignant tumor involving the central nervous system
- Severe psychiatric disease (e.g., schizophrenia)
- Bilateral hemiparesis or infarcts to the primary motor cortex or the corticospinal tract in the hemisphere ipsilateral to the hemiparesis
- Pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions affecting the primary motor cortex or the corticospinal tract, excluding minor small vessel disease changes (e.g., clinically asymptomatic lacunae <1cm)
- Known brain lesion (surgical, traumatic)
- Evidence for enhanced cerebral pressure
- Severe cardiac dysfunction
- Life expectancy < 12 months
- NIHSS Score at enrolment > 20
- Blood glucose imbalances resistant to treatment (<50 mg/dl or >300 mg/dl)
- Elevated blood pressure resistant to treatment (RR > 185/110mmHg)
- Systemic thrombolysis using r-tPA or thrombectomy within the last 24 hours before enrolment in the study
- Medication with benzodiazepines, high-potency antipsychotics, or tricyclic antidepressants before hospitalization or long-term during hospitalization

*Outcome measures*

The primary endpoint of this study is relative grip strength defined as of the maximum grip strength of the affected (paretic) hand compared to the unaffected hand, assessed three to six months after the intervention, i.e., in the chronic phase post-stroke. While motor recovery after stroke may be assessed with several measures, we selected grip strength based on the following rationale: First, relative grip strength represents a fundamental feature of hand motor function. Second, the assessment of grip strength can be conducted efficiently at the bedside, even in severely affected patients. A stroke leading to hemiparesis typically reduces grip

strength. In turn, recovery of grip strength usually precedes the recovery of other motor domains such as dexterity or movement speed [49].

Furthermore, improvements in grip strength predominantly reflect the restitution of neurological function as grip strength is less dependent on alternative movement strategies such as compensatory movements. Besides, grip strength is mediated by contralateral M1 activity [50]. Therefore, given that in the present study iTBS is applied to enhance M1 activity, grip strength seems to be a sensitive readout to monitor improvements of M1. Finally, as the present study is designed based on a pilot study that also used grip force as the primary outcome parameter [24], we aimed at reproducing the beneficial effects of iTBS on the recovery of grip force. Besides, we further assess the impact of iTBS on the motor recovery in other parameters frequently used to study motor performance after stroke. These secondary endpoints comprise different measures of gross and fine upper limb function assessed by the Action Research Arm Test (ARAT [51]) and the Fugl-Meyer Motor Scale (FM [52]) of the upper extremity, stroke severity measured by the National Institutes of Health stroke scale (NIHSS), general disability (modified Rankin Scale, mRS [53]), and quality of life (EuroQol 5D including the visual analogue scale, EQ-5D). Moreover, in order to obtain electrophysiological measures of corticospinal integrity, motor evoked potentials (MEP) and the RMT of the ipsilesional M1 are included as secondary endpoints. Finally, to account for differences in rehabilitation treatments between completion of the intervention (T9) and the follow-up assessment (T10), we document the performance in activities of daily living assessed by the Barthel scale as well as the duration of stay in external rehabilitation facilities.

In sum, these tests provide a detailed assessment, monitoring the clinical and electrophysiological condition of patients before and after iTBS (Table 2).

*Randomization and stratification*

After obtaining informed consent, randomization is performed using the 24/7 online

randomization tool ALEA (FormsVision BV, Abcoude, NL). Patients are allocated 1:1 into the intervention groups, receiving “verum” or “control” iTBS. In order to balance groups regarding potential confounding factors, randomization is stratified based on patients’ age (≤ 68, >68 years), motor impairment (relative grip strength < 10%, 10 – 70%, > 70%), and stimulation intensity (≤ 50%, > 50% maximal stimulator output), as these factors are known to impact on motor recovery post-stroke [54,55].

*Statistical analysis*

After data collection, confirmatory and descriptive analyses will be conducted. In our proof-of-principle study, we obtained data from a smaller sample [22], which revealed three to six months after the intervention an increase of grip strength of 38.1 ± 28.7 % in patients treated by iTBS versus 26.2 ± 11.7% in the control stimulation group. Thus, the observed effect strength amounted to 0.54. Using an unpaired t-Test with a two-sided 5% type I error and a power of 80%, a sample of 110 patients is required (calculated using the software G*Power 3.1.7). Assuming a drop-out rate of 25% based on the cohort of Volz and colleagues (2016), an estimated sample of 150 recruited patients is needed.

Variables are analyzed descriptively using mean, standard deviations, quantiles (0, 25, 50, 75, 100), or count and frequency, respectively. The final statistical analysis is carried out in an intention to treat (ITT) collective including all patients who received at least one intervention (verum or control) with a subsequent grip strength testing, to assess the safety and efficacy of iTBS. Moreover, a supportive analysis is performed based on the “per protocol” (PP) collective, which includes all patients who underwent at least five [24] interventions (verum or control) and provided grip force measures at baseline and the three to six months follow-up.

The primary endpoint, i.e., the change in grip strength after three months (T10), is analyzed using a linear mixed model with repeated measurements, in which the factors group (verum, control), time, group x time, and strata at baseline (age, motor impairment, stimulation intensity) will be entered. Moreover, the model will account for the number of data points obtained during the intervention phase (T1 – T9). The primary hypothesis is addressed using

a customized test (contrast) to compare the change from baseline (T0) to three to six months (T10) between the two treatment groups. Mean difference, corresponding 95% confidence interval, and the p-value (two-sided) will be presented.

All secondary variables will be analyzed similarly or using unpaired t-tests or Mann-Whitney U tests, respectively. (Serious) Adverse events are listed. Subgroup analyses will be performed for randomization stratification variables and length of rehabilitation therapy. The current version of SPSS Statistics (IBM Corp., Armonk, NY, USA) will be used for the statistical analyses.

*Blinding*

The study is carried out using a double-blinded design, in which neither the patients nor the testing physicians or statisticians are aware of the intervention arm (verum or control). As applying iTBS over different stimulation sites (depending on the patients' intervention arm) implicates that physicians performing the intervention cannot be blinded, the intervention team needs to be separated into blinded physicians performing patient recruitment and examinations, and unblinded physicians exclusively applying iTBS. Thereby, we ensure that both patients and investigators are blinded during the assessment of outcome parameters throughout the entire study procedure. In the case of an emergency unblinding, investigators at the Department of Neurology have access to sealed envelopes labelled with the patients' randomization numbers. To maintain the quality of the trial, a patient's allocation should only be unblinded in exceptional circumstances when knowledge of the actual treatment is essential for the management of the patient.

*Safety*

The exclusion criteria of the present trial follow the latest safety recommendations for rTMS [44,48], thereby reducing the risk of adverse events or reactions to iTBS to a minimum.

Adverse events (AE) or serious adverse events (SAEs) are assessed throughout the entire observation period of the study, including all scheduled visits T0 – T10. All events are reported to the federal authorities (Federal Institute for Drugs and Medical Devices, BfArM). In our pilot study [24], no severe adverse event occurred, especially no focal or generalized seizures.

*Documentation and quality assurance*

All data assessed during the trial are documented promptly after data acquisition and entered into the electronic case report form (eCRF) by the responsible investigators. Regular monitor inspections ensure high quality of documentation and the correct implementation of the study protocol. The Clinical Trials Centre Cologne (CTCC Cologne) is responsible for the monitoring. Besides the initiation visit at the beginning and the close-out visit at the end of the study, monitoring visits are performed on average after every tenth patient included. Thus, at least 15 visits are scheduled. Monitoring visits include a review of source data documented in the eCRF, written consent, inclusion and exclusion criteria.

*Data collection and management*

CTCC Cologne performs the data management. The commercial online software TrialMaster™ (OmniComm.com) is used as a data management system, ensuring data safety by a firewall and backup system, including multiple data storage sites. The database was developed and validated by the CTCC Cologne.

All data collectors are stroke-specialized neurologists who have been trained in good clinical practice (GCP). After the investigators enter the data into the eCRF, the CTCC Cologne reviews the data for completeness and plausibility. The data manager and investigators resolve discrepancies and implausible entries.

Only researchers involved in the data collection, management and data analysis will have access to the final dataset. However, the principal investigator allows direct access to all source data and documents at monitoring, and inspection from federal authorities (Federal Institute for Drugs and Medical Devices, BfArM).

## Ethics and dissemination

The Ethics Commission of the Faculty of Medicine of the University of Cologne approved this protocol and its amendments (reference number 15 - 343). The amendments leading to the current version (version 3, November 15th 2018) were made to increase the number of patients participating in the study. By better specification of the exclusion criteria, more patients can be included without additional safety concerns. Before entering the study, all participants are informed that their participation is entirely voluntary, and that their withdrawal of consent is possible at any time without further consequences. All requirements regarding the well-being, insurance, rights, and privacy of participants are fulfilled. The study findings will be reported at conferences and in peer-reviewed journals.

## Trial status

At the time of submission, recruitment has not been completed.

## Abbreviations

AE: adverse event, AMT: active motor threshold, ARAT: Action Research Arm Test, CTCC: Clinical Trials Center Cologne, eCRF: electronic case report form; rTMS: repetitive Transcranial magnetic stimulation; EV: Evaluation visit, FM: Fugl-Meyer Motor Scale of the upper extremity, GCP: good clinical practice, iTBS: intermittent theta-burst stimulation, M1: primary motor cortex, MEP: motor evoked potential, mRS: modified Rankin Scale, NIHSS: National Institutes of Health stroke scale, tDCS: transcranial direct current stimulation, RCT: randomized controlled trial, RMT: resting motor threshold, r-tPA: recombinant tissue-type plasminogen activator, SAE: serious adverse event



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## Author contributions

CG, LH, LJV, and GRF developed the study design and wrote the statistical analysis plan in collaboration with DK and SH. LH, CR, CG, and GRF perform the clinical evaluation. CT conducts rTMS interventions. LH and CG wrote the first draft of the manuscript. CT, LJV, and GRF revised it for intellectual content. All authors read and approved the final manuscript.

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## Competing interests

None of the authors have anything to disclose.

## Ethics approval and consent to participate

The Ethics Commission of the Medical Faculty of the University of Cologne (reference number 15 - 343) approved the study and its amendments:

First approval November 2nd 2015 (original version).

Amendment (version 2.22) approved and implemented December 20th 2016. Specification of exclusion criteria.

Amendment (version 3) approved and implemented November 15th 2018. Change of inclusion and exclusion criteria.

Written informed consent is obligatory before study participation. The study is registered at the German Clinical Trials Register (DRKS, www.drks.de, DRKS-ID: DRKS00008963) and the ClinicalTrials.gov database (Identifier: NCT02910024).

## Data sharing statement

The data collected in this study are available from the corresponding author upon reasonable request after the first manuscript has been published.

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**Table 1**

| Trial characteristics based on WHO trial registration dataset | |
|---|---|
| Data category | Trial information |
| Primary registry and trial identifying number | German Clinical Trials Register (DRKS)<br>DRKS-ID: DRKS00008963 |
| Date of registration in primary registry | 2016 - February - 16 |
| Secondary identifying numbers | ClinicalTrials.gov (NCT02910024) |
| Source(s) of monetary or material support | The study is conducted as an investigator initiated study supported by the Max-Delbrück Prize to GRF and by the University of Cologne Emerging Groups Initiative (CONNECT group; CG and GRF) implemented into the Institutional Strategy of the University of Cologne and the German Excellence Initiative. |
| Primary sponsor | University of Cologne, Albertus-Magnus-Platz 50923 Cologne |
| Secondary sponsor | NA |
| Contact for public queries | Prof. Gereon R. Fink (gereon.fink@uk-koeln.de) |
| Contact for scientific queries | Prof. Gereon R. Fink (gereon.fink@uk-koeln.de) |
| Public title | Theta-Burst-Stimulation in early Rehabilitation of Stroke |
| Scientific title | Theta-Burst-Stimulation in early Rehabilitation of Stroke |
| Country of recruitment | Germany |
| Healthy conditions(s) or problems studied | Stroke with hemiparesis including impaired hand motor function |
| Interventions | Active Comparator: Real-rTMS<br>Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex in the lesioned hemisphere using the intermittent theta-burst-stimulation protocol (iTBS; application of 3 pulses with a frequency of 50 Hz, in a theta-rhythm of 5 Hz for 2 seconds, repeated every 10 seconds, duration of one session: about 3,5 minutes) before physiotherapy for 8 days<br><br>Sham Comparator: Sham-rTMS<br>Repetitive transcranial magnetic stimulation (rTMS) in sham position (tilted coil over parieto-occipital vertex) before physiotherapy for 8 days |
| Key inclusion and exclusion criteria | Inclusion Criteria: written consent, age: 40-90 years, ischemic stroke, hemiparesis with impaired hand motor function<br>Exclusion Criteria: Subjects who are legally detained in an official institute (§20 MPG), participation in clinical trial within the last 12 weeks, electronic implants or ferromagnetic Implants located in the head, neck or thorax (e.g. clips, intracranial shunt, artificial heart valve, pacemaker), medication pump (e.g. insulin pump), metal splinters in eye or head, pregnancy / breastfeeding, severe neurodegenerative disease, severe neuro-inflammatory disease, history of seizures / epilepsy, physical addiction to alcohol, medication, or drugs (excluded: nicotine), insufficient compliance, present or past malignant tumor involving the central nervous system, severe psychiatric disease, clinically |

| | |
|---|---|
| | manifest bilateral hemiparesis or infarcts in the primary motor cortex or along the corticospinal tract in the hemisphere ipsilateral to the hemiparesis, pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions in the primary motor cortex or along the corticospinal tract, excluding microvascular changes (e.g. clinically asymptomatic lacunae <1cm), known brain lesion (surgical, traumatic), evidence for enhanced cerebral pressure, severe cardiac dysfunction, life expectancy < 12 months, NIHSS Score > 20, blood glucose imbalances resistant to treatment (<50 mg/dl or >300 mg/dl), elevated blood pressure resistant to treatment (RR > 185/110mmHg), systemic thrombolysis using rt-PA or thrombectomy within the last 24 hours before enrollment in study, medication with benzodiazepines, high-potency antipsychotics or tricyclic antidepressants before hospitalization or long-term during hospitalization |
| Study type | Interventional<br>Allocation: randomized intervention model.<br>Masking: double blind (subject, caregiver, investigator, outcomes assessor)<br>Assignment: parallel<br>Primary purpose: treatment |
| Date of first enrolment | April 2016 |
| Target sample size | 150 |
| Recruitment status | Recruiting |
| Primary outcome(s) | Relative grip force (time frame: three to six months after enrollment) |
| Key secondary outcomes | Relative grip force (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Action Research Arm Test (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Fugl-Meyer Motor Scale of the upper extremity (time frame: after 8 days of intervention, and three to six months after enrollment)<br>National Instituts of Health Stroke Scale (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Modified Rankin Scale (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Motor evoked potential induced by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Resting motor threshold as measured by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and three to six months after enrollment)<br>EuroQol 5D questionnaire (time frame: after 8 days of intervention, and three to six months after enrollment)<br>Barthel-Index at admission and discharge in external rehabilitation facility (time frame: three to six months after enrollment)<br>Days of rehabilitation after intervention phase (time frame: three to six months after enrollment) |

**Table 2**

| Study period | Pre-enrollment | T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visits | | | | | | | | | | | | |
| Screening (in-/exclusion criteria) | X | | | | | | | | | | | |
| Written informed consent | | X | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | |
| Medical history | X | X | | | | | | | | | | |
| Neuroimaging (MRI/CT) | X | | | | | | | | | | | |
| TMS-intervention (M1 iTBS/control iTBS) | | | X | X | X | X | X | X | X | X | | |
| Physiotherapy | | | X | X | X | X | X | X | X | X | | |
| Assessment of adverse events | | X | X | X | X | X | X | X | X | X | X | X |
| Relative grip strength | X | X | X | X | X | X | X | X | X | X | X | X |
| Documentation of medication | | X | X | X | X | X | X | X | X | X | X | X |
| Neurological examination | X | X | | | | | | | | | X | X |
| Electrophysiological examination (RMT, MEPs) | | X | | | | | | | | | X | X |
| Upper limb motor function (ARAT, FM) | | X | | | | | | | | | X | X |
| Stroke severity (NIHSS) | | X | | | | | | | | | X | X |
| Disability (mRS) | | X | | | | | | | | | X | X |
| Quality of life (EQ-5D) | | X | | | | | | | | | X | X |
| Assessment of external rehabilitation time | | | | | | | | | | | | X |

RMT: resting motor threshold; MEPs: Motor evoked potentials; ARAT: Action Research Arm Test; FM: Fugl-Meyer Motor Scale of the upper extremity; NIHSS: National Institutes of Health stroke scale; mRS: modified Rankin Scale; EQ-5D: EuroQol 5D including the visual analogue scale

## Figure legends

**Figure 1: Flow chart of study Procedure**

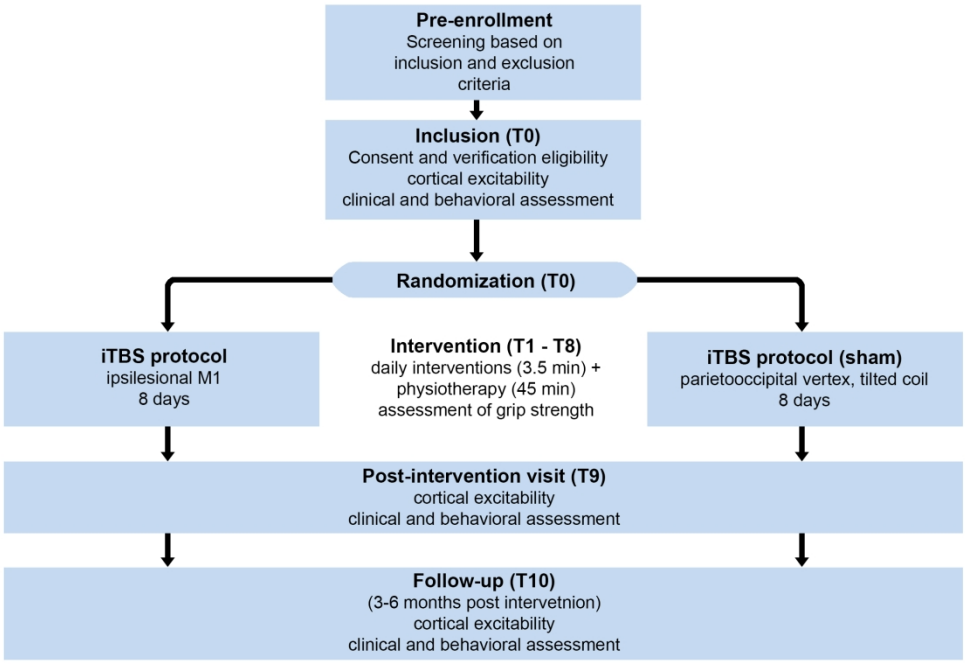


Figure 1. Flow chart of the study procedure

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 18 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 24-25 |
| Protocol version | #3 | Date and version identifier | 18 |
| Funding | #4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 17 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 18 |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-5 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 10 |
| Objectives | #7 | Specific objectives or hypotheses | 6-7 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 8-10 |

| | | | |
|---|---|---|---|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 8 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 13-14 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 10 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 26 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 11 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 11 |

| | | | |
|---|---|---|---|
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 11 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 11 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 14 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13-14 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11-12 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11-12 |

| | | | |
|---|---|---|---|
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 11-12 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 18 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 18 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13-14 |

| | | | |
|---|---|---|---|
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 14 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 2 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |