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## Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-SCI) – protocol of a prospective one-armed multi-centre study

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	ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, Clinical trials < THERAPEUTICS

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3 1 Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-  
4 SCI) – protocol of a prospective one-armed multi-centre study  
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36 Word count: 4374 words

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3 37 **ABSTRACT**  
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5 38 **Introduction:** Spinal cord injury (SCI) is a devastating condition with an immediate impact on  
6  
7 39 the individual's health and quality of life. Major functional recovery plateaus three to four  
8  
9 40 months after injury despite intensive rehabilitative training. To enhance training efficacy and  
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11 41 improve long-term outcomes, the combination of rehabilitation with electrical modulation of the  
12  
13 42 spinal cord and brain has recently aroused scientific interest with encouraging results. The  
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15 43 mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor  
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17 44 command and control centre, is considered a promising target for deep brain stimulation (DBS)  
18  
19 45 in patients with SCI. Animal experiments showed that MLR-DBS can induce locomotion in rats  
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21 46 with spinal white matter destructions of >85%.

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23 47 **Methods and analysis:** In this prospective one-armed multi-centre study we investigate the  
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25 48 safety, feasibility and therapeutic efficacy of MLR-DBS to enable and enhance locomotor  
26  
27 49 training in severely affected, subchronic and chronic AIS C patients in order to ultimately  
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29 50 improve functional recovery. Patients undergo an intensive training program with MLR-DBS  
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31 51 while being regularly followed-up until 6 months post-implantation. The acquired data of each  
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33 52 timepoint are compared to baseline while the primary endpoint is performance in the 6 Minute  
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35 53 Walking Test (6MWT). The clinical trial protocol was written in accordance with the SPIRIT  
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37 54 (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

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39 55 **Ethics and dissemination:** This first in-man study investigates the therapeutic potential of  
40  
41 56 MLR-DBS in SCI patients. Thus far, one patient has been implanted with electrodes and  
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43 57 underwent MLR stimulation during locomotion. Based on the preliminary results which promise  
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45 58 safety and feasibility, recruitment of further patients is currently ongoing. Ethical approval has  
46  
47 59 been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-  
48  
49 60 01104) and Swissmedic (10000316). Results will be published in peer-reviewed journals and  
50  
51 61 presented at scientific conferences.

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53 62 **Trial registration:** Registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017  
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55 63 (<https://www.clinicaltrials.gov>).  
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67 69 **Keywords:** Spinal cord injury, deep brain stimulation, mesencephalic locomotor region,  
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69 70 locomotion, training, rehabilitation  
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3 71 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 5 72 • This prospective one-armed multi-centre proof-of-concept study investigates the safety,  
6 73 feasibility and therapeutic potential of MLR-DBS to improve walking function after  
7 74 severe incomplete SCI.  
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9 75 • Patients with completed in-patient rehabilitation with highly limited ambulatory capacity  
10 76 are screened and considered for study enrolment.  
11  
12 77 • The study comprises a variety of clinical and electrophysiological assessments before,  
13 78 during, and after electrode implantation.  
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15 79 • Patients undergo intensive rehabilitative training with MLR-DBS and are followed-up  
16 80 on a regular basis until 6 months post-implantation.  
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18 81 • The primary endpoint is improvement of locomotion measured by the 6MWT 6 months  
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20 82 after electrode implantation compared to baseline performance.  
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## 84 INTRODUCTION

85 In the event of spinal cord injury (SCI) a person's life turns upside down within a split second,  
86 and a multitude of body functions are either severely impaired or completely lost instantly.  
87 Reacquiring lost functions including locomotion is of high importance for affected patients.[1]  
88 However, it remains a largely unmet medical need due to the lack of treatment options to  
89 sufficiently rewire interrupted fibre tracts and enhance repair of the damaged human spinal  
90 cord. Despite decades of basic research, neuro-rehabilitative training currently remains the  
91 only treatment option that increases the chances of long-term improvement of sensory-motor  
92 functions.[2,3] Even though most SCIs spare some descending and ascending fibre tracts,  
93 leaving the sublesional spinal cord [4] only incompletely disconnected from the brain, functional  
94 recovery remains limited in most cases.[3,5,6] The number of spared, descending fibres is  
95 often insufficient to convey appropriate control signals to sublesional locomotor circuits, e.g.  
96 central pattern generators (CPGs), which are thus deprived of supraspinal input and  
97 modulation,[7] and fail to induce rhythmic motor patterns.[8,9] However, these local rhythm  
98 generators remain functional and can be reactivated, e.g. by direct electrical stimulation in  
99 combination with training.[10–12] To increase the efficiency and efficacy of neurorehabilitation,  
100 locomotor training has therefore been combined with electrical epidural and transcutaneous  
101 stimulation of the spinal cord in small cohorts of patients in recent years, yielding promising  
102 results.[3,13–15] Another encouraging approach to recruit inactive, yet intact, sublesional  
103 motor circuits involves the electrical activation of spared descending reticulospinal tract fibres  
104 (Figure 1).[16] The majority of reticulospinal fibres arise from the medial medullary reticular  
105 formation, which relays the output of its upstream target, the mesencephalic locomotor region  
106 (MLR),[17–19] to the spinal cord. The MLR is a phylogenetically conserved key locomotor  
107 control centre in the brainstem, and is comprised of two main nuclei, the pedunculopontine  
108 (PPN) and the cuneiform nucleus (CNF).[20–22] The PPN is associated with exploratory  
109 behaviour,[23] and deep brain stimulation (DBS) of the PPN in patients with Parkinson's  
110 disease can result in a reversal of freezing of gait.[24–27] On the other hand, the CNF is known  
111 to be a main control region for locomotion initiation, maintenance and speed  
112 regulation.[23,28,29] Recently, the CNF has gained scientific and clinical interest as  
113 therapeutic target for DBS to improve deficient gait after SCI [16] and stroke.[30] Electrical  
114 activation of the MLR during locomotion has been shown to acutely improve hindlimb function  
115 during walking and swimming in a rodent model of severe but incomplete SCI.[16] DBS in  
116 humans is considered safe, reversible and minimally-invasive, and is being routinely and  
117 successfully applied in the treatment of various movement disorders.[31–36]  
118 Function and anatomy of the brainstem motor systems are highly conserved across  
119 mammalian species.[37] Due to their dispersed projection pattern throughout the spinal cord



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3 120 white matter,[38,39] reticulospinal fibres are likely to be partially spared after incomplete SCI  
4 121 in humans,[40] and are crucial for functional recovery after SCI.[41,42]

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6 122 Encouraging results from animal studies [16,30,43] have led to the initiation of a first in-man  
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8 123 study that investigates MLR-DBS enabled intensive rehabilitative training and its potential to  
9 124 enhance locomotion in non-ambulatory, subchronic and chronic SCI patients. The study  
10 125 protocol is presented in this article.

11  
12 126 We hypothesize that MLR-DBS can modulate the activity of spared reticulospinal fibres that  
13 127 bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network  
14 128 that supports walking (Figure 2). We propose that enhancing excitability of sublesional spinal  
15 129 motor circuits increases training efficacy and promotes recovery of motor function in patients  
16 130 with incomplete, subchronic and chronic SCI.  
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## 131 **METHODS AND ANALYSIS**

### 132 **Study design**

133 This prospective one-armed phase I/II multi-centre study is being conducted as cooperation of  
134 the University of Zurich, the University Hospital Zurich and the Balgrist University Hospital  
135 Zurich. Patients are screened and selected by SCI specialists and physiotherapists at the  
136 Balgrist University Hospital. Incomplete SCI is confirmed based on clinical examinations,  
137 magnetic resonance imaging (MRI), and electrophysiological measurements. After patient  
138 inclusion and baseline examinations, a DBS lead is stereotactically unilaterally implanted into  
139 the cuneiform part of the MLR, followed by infraclavicular or abdominal implantation of an  
140 impulse generator (IPG, Figure 3). The side of lead placement is chosen based on the  
141 functional and anatomical lesion extent, with preference for the less severely affected side to  
142 transmit as much descending brainstem motor signal as possible beyond the lesion via the  
143 primarily uncrossed reticulospinal fibres. The patients are followed-up on a regular basis until  
144 6 months post-implantation, and the acquired data of each timepoint are compared with  
145 baseline findings. The primary outcome measure for improvement of ambulation in this study  
146 is the difference in covered distance in the 6 Minute Walking Test (6MWT) at 6 months post-  
147 implantation compared to baseline level. The trial is considered successful if the patient's  
148 performance in the 6MWT 6 months after treatment start is at least 30% [44] higher compared  
149 to performance at baseline. For the design of the clinical trial protocol we followed the SPIRIT  
150 (Standard Protocol Items: Recommendations for Interventional Trials) checklist.[45]

### 151 **Study population**

152 Female and male patients (18-75 years) with completed in-patient rehabilitation and at least 6  
153 months of recovery after SCI are screened and considered for study enrolment. We aim at  
154 including 5 patients, who have to complete all preoperative and postoperative examinations  
155 until 6 months after electrode implantation, resulting in a total of 11 timepoints. In case of  
156 withdrawal of participation, dropouts and incomplete follow-up, we will include a maximum of  
157 2 additional patients (replacement of dropouts/withdrawal). The study is open to national and  
158 international patients. Basic understanding of German or English is required. Patients who  
159 prematurely withdraw from the study will be offered complete removal of all implanted material,  
160 and will be followed-up according to clinical standards. The patients' study related data will  
161 remain in the study.

### 162 **Inclusion and exclusion criteria**

163 To be eligible for the study, a participant must fulfil all inclusion criteria and none of the  
164 exclusion criteria (Table 1).

### 165 **Table 1 – Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
Informed consent	Enrolment of the investigator, her/his family members, employees and other dependent persons
Participation in two assessment sessions before enrolment (screening and baseline)	Limitation of standing and walking function based on accompanying (CNS) disorders
Willingness and ability to comply with the protocol and to attend required study training and visits	Cardiovascular disorders restricting physical training or peripheral nerve disorders
Female or male subject	Implanted technical devices (pacemaker, defibrillator, others)
Age 18-75	History of significant autonomic dysreflexia
Motor incomplete SCI	Cognitive disorders/brain damage
Level of lesion at or above T10, based on AIS level, preservation of sacral function	Drug refractory epilepsy
Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition (like haemorrhage, benign tumour)	Severe joint contractures disabling or restricting lower limb movements
Minimum 6 months of recovery after SCI	Haematological disorders with increased risk of bleeding during surgical interventions
Completed in-patient rehabilitation program	Participation in another study with investigational drug within 30 days preceding and during the present study
WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters	Congenital or acquired lower limb abnormalities (affection of joints and bone)
Stable medical and physical condition	Women who are pregnant or breast feeding or planning a pregnancy during the course of the study
Adequate care-giver support and access to appropriate medical care in patient's home community	Lack of safe contraception
	Inability of the participant to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc.
	Known or suspected non-compliance, drug or alcohol abuse
	Current or prior malignancy

166 CNS = central nervous system. SCI = spinal cord injury. AIS = ASIA (American Spinal Injury Association)  
 167 Impairment Scale. WISCI = Walking Index for Spinal Cord Injury. PI = principal investigator.

## 168 Target area definition

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3 169 While the rodent CNF and its microstructure are nowadays well characterized,[23,28,29] the  
4 170 human CNF is poorly described, and presented only in a very limited number of stereotactic  
5 171 atlases. However, due to the high phylogenetic conservation,[37] the CNF can be defined by  
6 172 surrounding landmarks and coordinates available from lead implantation into the PPN and  
7 173 rodent stereotactic atlases (Figure 4).

## 11 174 **Surgery**

13  
14 175 All individuals included in the study undergo unilateral frame-based (Riechert-Mundinger  
15 176 frame; Inomed, Emmendingen, Germany) stereotactic implantation of an intracranial lead  
16 177 (model 3389-28; Medtronic, Minneapolis, MN, USA) via a unilateral burrhole under local  
17 178 anaesthesia. The distal end of the DBS lead features narrow (0.5 mm) spacing between each  
18 179 of the four stimulation contacts of 1.5 mm length each. After mounting of the stereotactic frame,  
19 180 high resolution cranial computed tomography (CT) scans are performed and fused with the  
20 181 individual's MRI scan to retrieve stereotactic coordinates based on the pre-planned trajectory.  
21 182 Depending on the patient's preferences and the surgeon's decision, patients either receive a  
22 183 full implant consisting of a DBS lead, an extension and an IPG within one surgical session, or  
23 184 receive a lead only, which is externalized for maximal 10 days for evaluation of side effects  
24 185 and responsiveness to stimulation. In the latter scenario, the patient undergoes a second  
25 186 surgery with either removal of the lead (dropout of the study participant) or completion of the  
26 187 DBS system. For completion, the lead is connected to a Medtronic Activa SC model 37603  
27 188 IPG using a Medtronic model 37086-60 or 37086-95 extension cable. The IPG is implanted  
28 189 subcutaneously in the pectoral or abdominal region, respectively, depending on the patient's  
29 190 physiognomy and preference.

30 191 Intraoperatively, mapping of the CNF, behavioural and neurophysiological testing is performed,  
31 192 and different stimulation parameters (frequency, pulse width, stimulation intensity and  
32 193 voltages) are tested. Microelectrodes can be precisely inserted along a predefined trajectory  
33 194 aiming towards the CNF with the Neuro Omega neuromodulation system and manual drive  
34 195 (Alpha Omega Engineering, Nazareth, Israel) attached to the Riechert-Mundinger frame.  
35 196 During electrode insertion (0.5 mm steps), microelectrode recordings (30 s at each position)  
36 197 of single and multi-unit activity (local field potentials, LFPs) are performed during resting state,  
37 198 imagination of walking, passive and active lower limb movement within 10 mm prior and  
38 199 maximum 5 mm after the projected target point. Signals are band pass filtered (1-500 Hz). In  
39 200 case of a presumed elevated risk of haemorrhage, the surgeon can decide to exclusively use  
40 201 macroelectrodes instead of microelectrodes. In parallel, constant-frequency stimulation is  
41 202 performed while the patient performs a selection of motor tasks with the lower limbs hanging  
42 203 off the surgery table, accompanied by simultaneous electromyographic (EMG) recordings.  
43 204 Stimulation amplitude is slowly increased, and changes in range of motion with and without  
44 205 stimulation are measured by goniometers attached to knee and ankle while the patient

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3 206 performs rhythmic knee and ankle flexion/extension movements. Furthermore, speech and  
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5 207 cognition are tested with and without stimulation, and the appearance of side effects, in  
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7 208 particular pain sensations and paraesthesia, is closely monitored and documented. Additional  
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9 209 electrophysiological measurements, including motor evoked potentials (MEPs) and  
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11 210 somatosensory evoked potentials (SSEPs), are performed, and event related potentials  
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13 211 (ERPs) are analysed. Ultimately, the coordinates resulting in best motor performance (e.g.  
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15 212 greatest range of motion of knee joint, highest frequency of rhythmic knee flexions/extensions)  
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17 213 at the lowest stimulation parameters without provoking side effects are chosen, and the  
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19 214 quadripolar DBS lead is implanted, fixed to the skull, and either temporarily externalized or  
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21 215 connected to an extension and IPG. All subjects subsequently receive a postoperative cranial  
22  
23 216 CT scan to verify correct lead position and exclude surgery-associated complications (e.g.  
24  
25 217 haemorrhages). Each patient recovers from surgery in the intermediate care unit overnight.

## 218 **Clinical assessments**

### 219 6 Minute Walking Test (6MWT)

220 During the 6MWT,[44] the patient is asked to cover a maximal distance within 6 minutes on  
221  
222 even ground without any obstacles. The patient is accompanied by an experienced investigator  
223  
224 (i.e. physiotherapist) to prevent falling, and may rest at his own discretion and use a walking  
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226 aid (consistent across all timepoints). The distance covered (m), time and number of rests  
227  
228 (min, count) is documented. Each assessment is video recorded.

### 225 10 Meter Walking Test (10MWT)

226 The 10MWT [46] is a widely used assessment tool to measure maximal walking speed (m/s).  
227  
228 The patient is instructed to walk 10 m as quickly as possible, but safely, and is given 5 m for  
229  
230 acceleration and deceleration. Patients may use assistive devices (consistent across all  
231  
232 timepoints).

### 230 Timed-Up and Go Test (TUG)

231 The TUG is a basic evaluation tool of functional mobility. It measures the time (s) needed to  
232  
233 rise from a chair, walk 3 m, turn around and return to a seated position. Participants are asked  
234  
235 to perform the TUG at their self-selected normal speed, using their walking aid if required. The  
236  
237 timer is started on the command “ready–set–go” and stopped as the patient returns to a seated  
238  
239 position.

### 236 Kinematic assessment

237 Kinematic assessments are performed during over-ground and treadmill walking. Individuals  
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239 are secured using the FLOAT (“Free Levitation for Overground Active Training”),[47,48] a  
multidirectional overhead support system that allows patients to move in a large workspace

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3 240 that is equipped with a 3D motion capture system with infrared cameras (Vicon Motion Systems  
4 241 Ltd., Oxford, UK). The cameras are able to detect the position of reflective markers placed on  
5  
6 242 patients' anatomical landmarks, allowing the quantification of kinematic movement  
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8 243 characteristics.[49,50] Additionally, muscle activity is measured with an EMG setup (myon AG,  
9 244 Schwarzenberg, Switzerland). These measures allow the quantification of patients' walking  
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11 245 function with high precision and the comparison of gait patterns within (with and without DBS)  
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13 246 and between different sessions. In addition to walking assessments, maximal knee and ankle  
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15 247 range of motion is evaluated with and without stimulation with the motion capture system during  
16  
17 248 rhythmic flexion/extension tasks performed by the patient in supine or sitting position. Besides  
18  
19 249 quantitative assessment of locomotor function, the FLOAT allows patients to train diverse  
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21 250 activities such as level walking, running, stair manoeuvres, chair interactions or walking on  
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23 251 uneven terrain with and without stimulation at the limit of their abilities with tailored body weight  
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25 252 support.

#### 253 Long-term Monitoring of Physical Activity

254 For constant monitoring of physical activity during training and daily life, wearable, wireless  
255 sensors (<http://zurichmove.com/>) are mounted to the patient's wrists, ankles, and wheelchair.  
256 Data are transferred via SSL-encrypted links (<https>) established between sites (e.g. a patient's  
257 home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

#### 258 ASIA Impairment Scale (AIS)

259 The American Spinal Injury Association (ASIA) International Standards for Neurological  
260 Classification of SCI (ISNCSCI) [51] is an internationally used gold standard method of  
261 assessing the neurological status of an individual with SCI. The AIS is carried out by trained  
262 medical staff using the ISNCSCI worksheet (<https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/>).

#### 264 Modified Ashworth Scale (MAS)

265 The MAS [52] is a clinical scale used to assess muscle spasticity in patients with lesions of the  
266 central nervous system.

#### 267 Spinal Cord Independence Measure (SCIM III)

268 The SCIM is a reference tool for the assessment of overall functional ability after SCI. The last  
269 version (III) of SCIM contains 19 tasks organized into 3 subscales: Self-care, Respiration &  
270 sphincter management, and Mobility.[53] The combined scores on all 19 tasks result in an  
271 overall score ranging from 0 to 100, with higher scores reflecting greater functional ability.

#### 272 Walking Index for Spinal Cord Injury (WISCI II)

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3 273 The WISCI assesses walking function on an ordinal scale,[54] and captures the extent and  
4 274 nature of assistance a person with SCI requires to walk. Rating is performed according to  
5  
6 275 Ditunno et al.[54]  
7

8 276 Assessment of lower urinary tract (LUT) function  
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10  
11 277 To address the burden of neurogenic LUT dysfunction on patient's quality of life after SCI and  
12 278 to analyse the effect of MLR-DBS on recovery of LUT function, a combination of qualitative  
13 (bladder diary, QUALIVEEN questionnaire) and quantitative assessments (urodynamic  
14 279 measurements, renal ultrasound) of LUT function are applied in accordance to the European  
15 280 Association of Urology (EAU) Guidelines on Neuro-Urology.[55,56]  
17 281

18  
19 282 • Bladder diary: by completing the Three Day Bladder Chart [57] information on daytime  
20  
21 283 frequency, nighttime frequency, voiding (e.g. spontaneous), catheter use  
22  
23 284 (transurethral, suprapubic, self-catheterization), voided volume, post void residual  
24  
25 285 volume, incontinence episodes, pad use, fluid intake and amount of urine per 24 hours,  
26  
27 286 and pain (visual analogue scale 0-10) is acquired.  
28

29  
30  
31 287 • QUALIVEEN questionnaire: all patients fill in the QUALIVEEN questionnaire for self-  
32  
33 288 judgement of LUT dysfunction according to Costa et al.[58]. Scores (0-4) are recorded  
34  
35 289 for "Limitations", "Constraints", "Fears" and "Feelings", and the calculated arithmetic  
36  
37 290 mean is transformed into values of 0-100.  
38

39  
40 291 • Urodynamic assessments: Cystometry, uroflowmetry, pressure-flow studies,  
41  
42 292 electromyography and video-urodynamics provide objective information on functioning  
43  
44 293 of the LUT and pelvic floor. Parameters retrieved are: cystometric capacity (mL),  
45 294 compliance (mL/cmH<sub>2</sub>O), detrusor overactivity (y/n), bladder volume at detrusor  
46  
47 295 overactivity (mL), maximum detrusor pressure amplitude (cmH<sub>2</sub>O) during storage  
48  
49 296 phase, urinary incontinence, maximum detrusor pressure (cmH<sub>2</sub>O) during voiding  
50  
51 297 phase, detrusor pressure at maximum flow rate (cmH<sub>2</sub>O), maximum flow rate (mL/s),  
52  
53 298 voided volume (mL), post-void residual (y/n and mL), pelvic floor electromyographic  
54  
55 299 activity (normal/abnormal), vesico-uretero-renal reflux (y/n).

56 300 • Renal and bladder ultrasound: indirect assessment of LUT function, e.g. via post-void  
57 301 residual volume, detrusor thickness or distension of the renal pelvis or ureter.  
58

59 302 Assessment of sexual function  
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3 303 The Female Sexual Function Index (FSFI) [59,60] is gold standard for the evaluation of female  
4 304 sexual function in clinical trials. It is questionnaire-based and contains 19-items including  
5 305 sexual arousal, orgasm, satisfaction and pain (score 2-80). The International Index of Erectile  
6 306 Function (IIEF) [61] is a standardized 15-item self-evaluation scale for male patients assessing  
7 307 erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and in  
8 308 general.

#### 13 309 Epworth Sleepiness Scale (ESS)

15 310 The ESS [62] measures a patient's general level of daytime sleepiness. The patient rates the  
16 311 probability of falling asleep on a scale of increasing probability (0-3) for eight different  
17 312 situations.

#### 21 313 Fatigue Severity Scale (FSS)

23 314 The FSS [63] evaluates the impact of fatigue based on a short questionnaire containing nine  
24 315 statements rating the severity of fatigue symptoms.

#### 27 316 Pain assessment

29 317 The EMSCI (European Multicenter Study About Spinal Cord Injury) pain assessment form  
30 318 (EPAF) [64,65] and the Spinal Cord Injury Pain Instrument (SCIPI) [66–68] are standardized  
31 319 and validated tools to evaluate pain in individuals with SCI.

#### 34 320 Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP)

36 321 The GRASSP [69,70] is a standardized upper-limb impairment measure specifically used to  
37 322 assess recovery of upper limb function (strength, sensation, prehension) in individuals with  
38 323 complete or incomplete tetraplegia.

#### 42 324 Short Form Health Survey to Assess Quality of Life (SF-36)

44 325 Patients with SCI experience tremendous changes in several aspects of everyday life and thus  
45 326 quality of life (QoL) [71] assessments are crucial in clinical trials. We employ the SF-36 [72], a  
46 327 multi-purpose, short-form health survey comprised of 36 questions that compares the relative  
47 328 burden of diseases and differentiates the health benefits produced by a wide range of different  
48 329 treatments. It yields an 8-scale profile of functional health and well-being scores,  
49 330 psychometrically based physical and mental health summary measures, and a preference-  
50 331 based health utility index. QoL is expressed as a score ranging from 0 to 100.

#### 56 332 **Electrophysiological assessments**



1  
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3 333 Electrophysiological assessments are performed in addition to clinical examinations as they  
4 334 allow prediction of functional outcome and help objectify the extent of the spinal lesion, its  
5 335 stability and potentially recovery of specific functions after SCI.[73,74]  
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8 336 Short-latency somatosensory evoked potentials (SSEPs)  
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10 337 SSEPs are performed to evaluate transmission of ascending signals within the dorsal column  
11 338 of the spinal cord and thus sensory function. The patient is in supine position, and stimulating  
12 339 electrodes are placed on the posterior tibial nerve (below the internal malleolus). Four  
13 340 subcutaneous recording electrodes are placed as follows: at L2 and L5, on the scalp (reference  
14 341 Fz and active Cz', 2 cm behind Cz), and a ground around the ankle. Cortical recording  
15 342 electrodes are positioned in accordance with the International 10–20 system.[75] Stimulation  
16 343 parameters are 200  $\mu$ s, up to 100 mA at a frequency of 3.1 Hz. The signal is recorded between  
17 344 30 and 300 Hz with 50 Hz notch filter. Waveforms are measured after 200-800 averages.  
18 345 Dorsal horn negativity (N24) is measured on the lumbar derivation (L5-L2) and represents  
19 346 peripheral conduction time. The post-Rolandic positivity (P45) is measured on the scalp  
20 347 derivation and represents the total conduction time. All measures are recorded before and after  
21 348 interventions. Response latency (ms) and amplitude ( $\mu$ V) are compared between timepoints  
22 349 and conditions (stim/no stim).  
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31 350 DBS evoked potentials (DBS-EPs)  
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34 351 DBS-EP testing is performed similar to SSEP measurements. However, instead of stimulating  
35 352 a peripheral nerve, the evoked cortical response is generated by repetitive low frequency  
36 353 stimulation of the target region (CNF/MLR). Outcome measures are response latency (ms) and  
37 354 amplitude ( $\mu$ V).  
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41 355 Motor evoked potentials (MEPs)  
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43 356 MEPs are tested to evaluate the ability of MLR-DBS enhanced training to induce remodelling  
44 357 of spinal pathways leading to amplification of descending signals. Surface recording electrodes  
45 358 are positioned on the tibialis anterior and the gastrocnemius medialis muscles. Transcranial  
46 359 magnetic stimulation (TMS) is applied on the scalp close to Cz and on the lumbar spine in front  
47 360 of L5. After a test stimulus, the stimulation is increased stepwise up to 100% of the stimulator  
48 361 output and the response is recorded under 5-10% voluntary muscle activation. Total  
49 362 conduction time is measured after scalp stimulation and peripheral conduction time after  
50 363 lumbar stimulation. All measures are recorded before and after interventions. Response  
51 364 latency (ms) and amplitude ( $\mu$ V) are compared between timepoints and conditions.  
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58 365 Local field potentials (LFPs)  
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3 366 LFPs are measured intraoperatively during probe insertion and postoperatively in case of  
4 367 temporary externalization of the lead. Intraoperative LFPs are measured in the target region,  
5 368 starting 10 mm above the target and ending 5 mm below the target. Postoperative  
6 369 measurements are performed at the 4 contacts of the implanted lead. Signals are band pass  
7 370 filtered (1-500 Hz).

#### 11 371 Electroencephalogram (EEG)

13  
14 372 To reconstruct patterns of specific neuronal activity and their change upon MLR-DBS, non-  
15 373 invasive EEG recordings are performed in the perioperative period and at the last assessment  
16 374 timepoint.

#### 19 375 **DBS during behavioural testing and rehabilitative training**

21 376 In the first two weeks after lead implantation, different stimulation parameters (frequency, Hz;  
22 377 pulse width,  $\mu$ s; amplitudes, mV) are tested during rest and locomotor training in order to  
23 378 identify optimal stimulator settings including safety limits for each patient individually.  
24 379 Subsequently, four combinations of parameters eliciting the best motor responses without side  
25 380 effects are chosen and programmed to the patient programming device (programs A-D).  
26 381 Afterwards, the patient undergoes intensive, rehabilitative training with his favourite program  
27 382 (e.g. 20 Hz, 420  $\mu$ s, suprathreshold intensity). Behavioural testing is performed with and  
28 383 without stimulation during each follow-up visit using the stimulation parameters applied during  
29 384 training.

#### 36 385 **Study endpoints**

38 386 The primary endpoint of the DBS-SCI study is improvement of locomotor function, represented  
39 387 by an increased distance covered during the 6MWT when comparing performance at the 6  
40 388 months timepoint with and without DBS with performance at baseline. Additionally, a variety of  
41 389 secondary endpoint assessments are performed (Table 2). Table 3 summarizes timing and  
42 390 schedule of the respective primary and secondary endpoint assessments.

47 391

392 **Table 2 – Primary and secondary endpoint measures.**

Primary endpoint measure	Secondary endpoint measures
6 Minute Walking Test (6MWT) at 6 months follow-up vs. baseline	6 MWT at follow-up timepoints other than 6 months post-implantation
	10 Meter Walking Test (10MWT)
	Timed Up and Go Test (TUG)
	Kinematic assessments (FLOAT)
	Spinal Cord Independence Measure (SCIM III)
	Walking Index for Spinal Cord Injury (WISCI II)
	Activity counts (patient's overall activity level)
	Electrophysiological measurements*
	Quality of life (SF-36)
	Lower urinary tract (LUT) function**
	Sexual function (FSFI/IIEF)
	Spasticity (MAS)
	Neurological classification of SCI (AIS)
	Upper limb function (GRASSP)
	Level of fatigue (FSS)
	Level of sleepiness (ESS)
	Pain (EPAF, SCIPI)

393 FLOAT = Free Levitation for Overground Active Training. MLR = mesencephalic locomotor region.

394 \*Local field potentials (LFPs); somatosensory evoked potentials (SSEPs); motor evoked potentials  
 395 (MEPs); DBS evoked potentials (DBS-EPs); electroencephalogram (EEG). SF-36 = Short Form Health  
 396 Survey to Assess Quality of Life. \*\*bladder diary, QUALIVEEN questionnaire, urodynamic  
 397 measurements, bladder and renal ultrasound. FSFI = Female Sexual Function Index. IIEF =  
 398 International Index of Erectile Function. MAS = Modified Ashworth Scale. AIS = American Spinal Injury  
 399 Association (ASIA) Impairment Scale. GRASSP = Graded Redefined Assessment of Strength,  
 400 Sensation and Prehension. FSS = Fatigue Severity Scale. ESS = Epworth Sleepiness Scale. EPAF =  
 401 EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal  
 402 Cord Injury Pain Instrument.

403 **Table 3 – Flowchart summarising scheduling and timing of primary and secondary**  
 404 **endpoint assessments.**

Site	Study periods	Screening	Baseline	DBS surgery	Post-implantation phase			IPG implantation	Rehabilitation / Follow-up phase							
		Visit	1	2	3	4	5	6*	7*	8	Dis-charge	Site	9	10	11	
Day (d) / month (mo)		-90 to -30 d	-10 to -1 d	0	1 to 3 d	4 to 7 d	8 to 9 d	6 to 10 d	14 d +/-3 d			mo 1 +/-3 d	mo 3 +/-1 week	mo 6		
<b>Study inclusion and consent</b>																
University Hospital Zurich/ Balgrist University Hospital	Consenting		X													
	Enrolment	X														
	Patient inclusion by PI		X													
	<b>Imaging</b>															
	X-ray thorax		X								X					
	X-ray skull, abdomen										X					
	Stereotactic cranial CT				2 X											
	Diagnostic MRI (3T)		X													
	<b>Perisurgical examinations</b>															
	Surgical examination (incl. wound check)		X		X	X	X	X	X				X	X	X	
	Anaesthesiologic examination			X	X			X	X							
	Neuropsychological assessment		X												X	
	Psychiatric assessment		X												X	
	<b>Surgical procedures</b>															
	DBS lead implantation				X											
	Implantation of IPG or explantation of DBS lead					X (externalization may be skipped and IPG implanted at visit 3)										
Education in handling of patient programming device										X						
<b>Electrophysiological assessments</b>																
EMG		X		X								X	X	X		
Microelectrode recording				X												
Nerve conduction		X												X		
Non-invasive EEG		X		X	X	X								X		
MEP, SSEP		X		X	X	X								X		
LFP, DBS-EP				X	X	X										
<b>Clinical assessments</b>																
Balgrist University Hospital	AIS	X	X				X			X		X	X	X	X	
	WISCI II	X	X				X			X		X	X	X	X	
	SCIM III	X	X				X			X		X	X	X	X	
	TUG	X	X				X			X		X	X	X	X	
	Kinematic assessments	X	X				X			X		X	X	X	X	
	6MWT	X	X				X			X		X	X	X	X**	
	10MWT	X	X				X			X		X	X	X	X	
	AE assessment		X		X	X	X	X	X	X		X	X	X	X	X
	Questionnaires: QoL, FSFI, IIEF, ESS, FSS, EAPAF, SCIPI		X										X	X	X	X
	Questionnaire: MAS	X	X					X					X	X	X	X
	LUT assessments (Bladder diary, QUALIVEEN, urodynamics, bladder/renal ultrasound)		X												X	
	GRASSP		X													X

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2  
3 405 \*If impulse generator (IPG) is implanted at visit 3, visit 6 and visit 7 will be skipped. \*\*Primary endpoint.  
4 406 DBS = deep brain stimulation. IPG = impulse generator. CT = computed tomography. MRI = magnetic  
5 407 resonance imaging. 3T = 3 Tesla. EMG = electromyography. EEG = electroencephalography. LFP =  
6 408 local field potentials. MEP = motor evoked potentials. SSEP = somatosensory evoked potentials. DBS-  
7 409 EP = DBS-evoked potentials. QoL = quality of life. FSFI = Female Sexual Function Index. IIEF =  
8 410 International Index of Erectile Function. ESS = Epworth Sleepiness Scale. FSS = Fatigue Severity Scale.  
9 411 AE = adverse event. AIS = American Spinal Injury Association (ASIA) Impairment Scale. WISCI II =  
10 412 Walking Index of Spinal Cord Injury. SCIM III = Spinal Cord Independence Measure. TUG = Timed Up  
11 413 and Go test. 6MWT = 6 Minute Walking Test. 10MWT = 10 Meter Walking Test. EPAF = EMSCI  
12 414 (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord  
13 415 Injury Pain Instrument. MAS = Modified Ashworth Scale. LUT = lower urinary tract function. GRASSP =  
14 416 Graded Redefined Assessment of Strength, Sensation and Prehension.

### 21 417 **Sample size**

22  
23 418 Based on data on the 6MWT [44,76,77] published in the literature and our clinical experience  
24 419 we estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment  
25 420 start compared to performance at baseline to be clinically relevant. A sample size of five  
26 421 patients provides us with a power (1- $\beta$ ) of 80% ( $\alpha = 0.05$ ). Founded on previous experience in  
27 422 DBS of the MLR,[78,79] we judge that the selected sample size will provide acceptable clinical  
28 423 validity for the study objectives.

### 33 424 **Statistical analysis**

34  
35 425 Considering the observational nature of this clinical trial, statistics will be restricted to  
36 426 descriptive statistics.

### 39 427 **Trial status**

40  
41 428 The study has started recruiting patients in March 2017. To date, one patient has been  
42 429 successfully included on November 26, 2018. Another patient has been included on March 15,  
43 430 2018, but withdrew consent prior to surgery (screening failure).

### 47 431 **Patient and public involvement**

48  
49 432 Patients or the public were not and will not be involved in the design, conduct, reporting, or  
50 433 dissemination plans of this research.

### 53 434 **ETHICS AND DISSEMINATION**

54  
55 435 The study was approved by the local institutional review board (IRB) of the Ethical Committee  
56 436 of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in  
57 437 January and March 2017. Protocol modifications have to be approved by the local IRB and  
58 438 communicated to trial registries. Before inclusion of a patient, the potential participant is

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3 439 informed orally by the investigator, and all potential participants are additionally provided with  
4 440 a clear and comprehensive information sheet. Sufficient time is given to the potential  
5 441 participant to decide whether to participate or not. If potential participants agree to participate  
6 442 in the study, they are asked to sign a consent form at the moment of inclusion in the study.  
7 443 The data obtained in the course of the study is treated according to the local data protection  
8 444 law and is handled in strictest confidence. During the study, subjects are identified solely by  
9 445 an anonymized patient identifier. The findings of this trial will be submitted to a peer-reviewed  
10 446 journal and abstracts are presented at relevant national and international scientific  
11 447 conferences. The study was registered on ClinicalTrials.gov (NCT03053791) on February 15,  
12 448 2017.  
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## 449 DISCUSSION

450 Encouraging results on behavioural effects of MLR-DBS in preclinical models of neurotrauma  
451 [16,30] have contributed to the initiation of this first in-man study, which is currently being  
452 carried out at the University Hospitals of Zurich. The primary aim of this study is to improve  
453 motor function and enable locomotion in wheelchair-bound, subchronic and chronic SCI  
454 patients with limited, non-functional ambulatory abilities with MLR-DBS, and to investigate the  
455 clinical feasibility and efficacy of MLR-DBS in humans. Ultimately, we aim at maximizing the  
456 long-term restitution of lost motor functions in patients with severe motor incomplete SCI. A  
457 first patient has been included and implanted successfully, followed by intensive locomotor  
458 training with suprathreshold MLR-DBS.

459 The most important lesson learnt from our previous experience in the treatment of this patient  
460 is that MLR-DBS is safe, feasible and well tolerated. No increase in pain, deterioration of  
461 residual motor or sensory functions, cognitive or emotional disturbances, increase in spasticity  
462 and no incontinence was observed. However, sufficient time has to be allocated to the  
463 adjustment of stimulation parameters for efficient training to ensue. Optimal stimulation  
464 parameters will have to be determined for each patient individually, however, wider pulses  
465 ( $>400\ \mu\text{s}$ ) seem to be more effective for enhancement of locomotion and more convenient than  
466 shorter pulse widths. LFP measurements and preliminary results from behavioural testing  
467 suggest that lower stimulation frequencies (8-20 Hz) are appropriate.

468 A particular challenge remains trajectory planning and lead implantation. Many regions of the  
469 brainstem, including the MLR subnuclei, are small and poorly described in humans when  
470 compared to the rodent PPN and CNF.[23,28,29] Coordinates known from DBS of the PPN  
471 with successful reduction of freezing of gait symptoms in patients with Parkinson's disease  
472 [24–27] can be adapted based on landmarks in human and rodent stereotactic atlases in order  
473 to localize the CNF in relation to the PPN. However, to increase the accuracy of planned  
474 trajectories and intraoperative targeting, a more detailed description of the macro- and  
475 microanatomy of the human MLR is urgently needed.

476 Another important step in trial design and treatment development is patient selection. In both  
477 rodents [16,42,80] and humans,[41] the reticulospinal system is crucial for functional recovery  
478 after SCI, and at least a small number of reticulospinal fibres needs to be preserved in order  
479 to reactivate lumbar CPGs via MLR-DBS. Thus, patients who have suffered an anatomically  
480 complete SCI are not envisioned eligible for MLR-DBS. Fortunately, the majority of SCIs are  
481 anatomically incomplete,[4] and reticulospinal fibres are likely to be at least partially spared  
482 after SCI in humans [40] due to their scattered projection pattern in the spinal cord white  
483 matter.[38,39] Based on preclinical data and experience gained from the first study participant  
484 we suggest that patients with an incomplete SCI and residual proprioceptive function, who are  
485 able to stand, but suffer from deficient stepping initiation and walking function are most likely

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3 486 to benefit from MLR-DBS-enabled and -enhanced training. To allow for an integration of the  
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5 487 effects of MLR-DBS into the still plastic spinal system during early phases of rehabilitative  
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7 488 training, we are currently adapting the original study protocol so that patients can be included  
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9 489 as early as 3 months after injury. Stratification of patients will be based on the expected  
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11 490 outcome of walking function predicted by the 6MWT. Patient recruitment and screening are  
12  
13 491 currently ongoing.

14 492 Our preliminary results from one study patient show that MLR-DBS is feasible and safe. The  
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16 493 efficacy of MLR-DBS to enhance training and promote functional recovery in human SCI  
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18 494 patients can now be tested in an appropriate number of individuals.  
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502 of the Balgrist University Hospital, the Institute for Regenerative Medicine of the University of  
503 Zurich, and the Swiss Federal Institute of Technology Zurich. The study has been presented  
504 at the “European Society for Stereotactic and Functional Neurosurgery (ESSFN) Meeting”  
505 2018 in Edinburgh, Scotland, and the “EANS Trauma & Critical Care Update meeting” 2018 in  
506 Lund, Sweden.

## 507 **Authors' contributions**

508 LHS and ASH contributed equally to the manuscript and are joint first authors. MES, LR, and  
509 ACu are joint senior authors. LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study,  
510 created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR  
511 perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function  
512 and perform testing and analysis. MS, MH, CRB, and LI designed and conduct  
513 electrophysiological measurements. TMK conceptualized and performs assessments of lower  
514 urinary tract function. IK and AP assist with study coordination and conduct questionnaire-  
515 based assessments. All authors are involved in the development and implementation of the  
516 study as well as in data collection and analysis. ASH and LHS designed the figures and drafted  
517 the manuscript. All authors critically revised the manuscript and approved its final version.

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519 Implanted hardware (electrodes, impulse generators, extension wires, and patient  
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527 not have any influence on study execution, data analysis, data interpretation, or decision to  
528 publish results.

## 529 **Competing interests**

530 The authors declare that they have no competing interests.

## 531 **Patient consent for publication**

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2  
3 532 Written informed consent for publication of clinical details and/or clinical images was obtained  
4 533 from the patient. A copy of the consent form is available for review by the editor of this journal.  
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7 534 **Ethics approval**

8 535 Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case  
9 536 number BASEC 2016-01104) and Swissmedic (10000316). Protocol modifications have to be  
10 537 approved by the local Ethical Committee of the Canton of Zurich and communicated to trial  
11 538 registries.  
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3 777 **FIGURE LEGENDS**  
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5 778 **Figure 1 - Schematic illustration of the reticulospinal system.** (A) Higher central nervous  
6 system centres of motion control send their signals to the mesencephalic locomotor region  
7 779 (MLR). The MLR is bilaterally linked to its downstream target, the gigantocellular reticular  
8 780 nucleus (NRG), which gives rise to the reticulospinal tract and drives the central pattern  
9 781 generators (CPG) for motoneuron activation and locomotion. (B-C) Horizontal section of the  
10 782 human (B) and cross section of the rat (C) midbrain at the level of the superior colliculi depicting  
11 783 the MLR (B – landmarks based on Afshar et al.[81]; C – landmarks based on Paxinos et al.[82]).  
12 784  
13 785 CNF = cuneiform nucleus. PPN = pedunculopontine nucleus.  
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3 787 **Figure 2 - Schematic illustration of MLR-DBS.** (A) After incomplete SCI, spared fibres of the  
4 788 reticulospinal tract are not sufficient to properly convey motor signals to sublesional locomotor  
5 789 circuits (CPG). The CPGs are thus deprived of their central input. However, these local rhythm  
6 790 generators remain intact. (B) MLR-DBS can recruit spared fibres of the reticulospinal tract  
7 791 system, enabling them to reactivate sublesional motor circuits. (C) Summary. MLR =  
8 792 mesencephalic locomotor region. NRG = gigantocellular reticular nucleus. SCI = spinal cord  
9 793 injury. CPG = central pattern generators. DBS = deep brain stimulation. (A-B) was modified  
10 794 from Hofer and Schwab, Curr Opin Neurol, 2019 [3], with permission.

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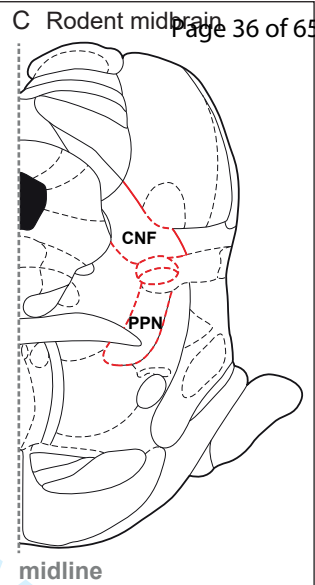
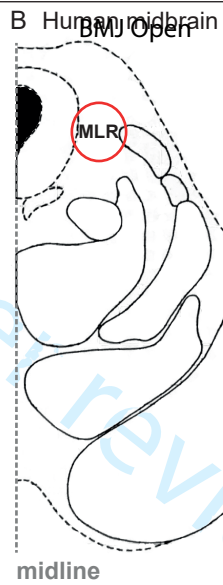
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3 796 **Figure 3 – Study timeline.** Patients with a motor incomplete SCI at the level of T10 or above  
4 797 and at least 6 months of recovery after injury are eligible to undergo screening for study  
5 798 participation. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance  
6 799 imaging, and electrophysiological measurements. 1-3 months after study enrolment, baseline  
7 800 testing is performed, followed by unilateral electrode implantation at the less severely affected  
8 801 side 1-10 days later. During surgery, the surgeon decides whether lead and impulse generator  
9 802 (IPG) will be implanted during one session, or whether the lead will be temporarily externalized,  
10 803 depending on intraoperative testing results. In case of lead externalisation, an evaluation  
11 804 period ensues where the patient's responsiveness to MLR-DBS and potential negative side  
12 805 effects are assessed. In case of unsatisfactory results or withdrawal of consent, the lead is  
13 806 removed, and the patient is registered as a study dropout. In case of satisfactory testing, the  
14 807 lead is internalized and the IPG is implanted. After complete implantation, follow-up testing  
15 808 ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged  
16 809 from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will  
17 810 undergo rehabilitative training with DBS at settings predefined during the first 2 weeks after  
18 811 implantation. SCI = spinal cord injury. mo = month(s). d = day(s). wks = weeks. FU = follow-  
19 812 up. TR = training. DBS = deep brain stimulation.

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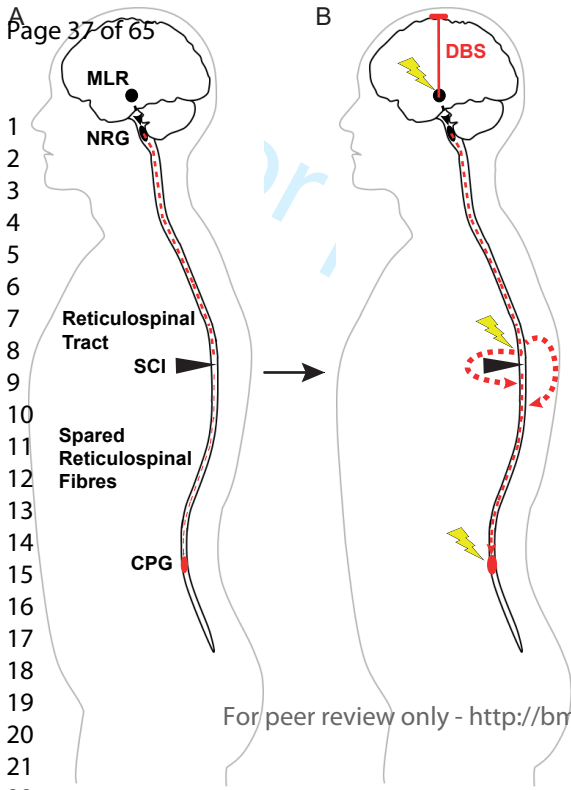
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3 814 **Figure 4 – Target area definition and electrode positioning.** The MLR can be targeted by  
4 815 aiming anterior to the inferior colliculi (IC), lateral of the periaqueductal grey (PAG), and slightly  
5 816 posterior to the central tegmental tract (CTT).[81,83] (A) Coronal, (B) axial, and (C) sagittal  
6 817 view of the mesencephalon of the first patient successfully included in the DBS-SCI trial,  
7 818 showing the localization of the implanted lead (red dot in light grey area). S = superior. I =  
8 819 inferior. L = left. R = right. A = anterior. P = posterior.  
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For peer review only

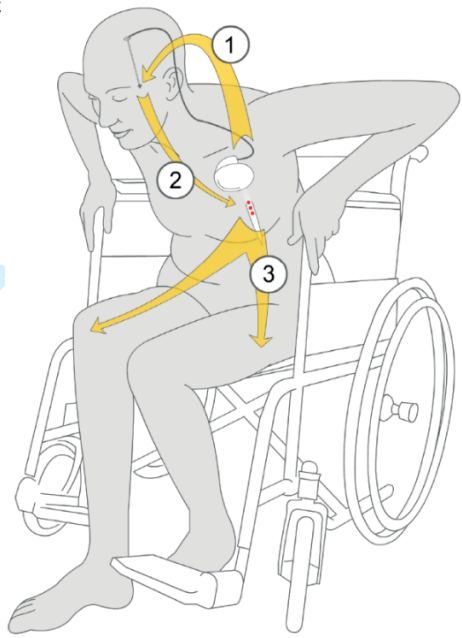
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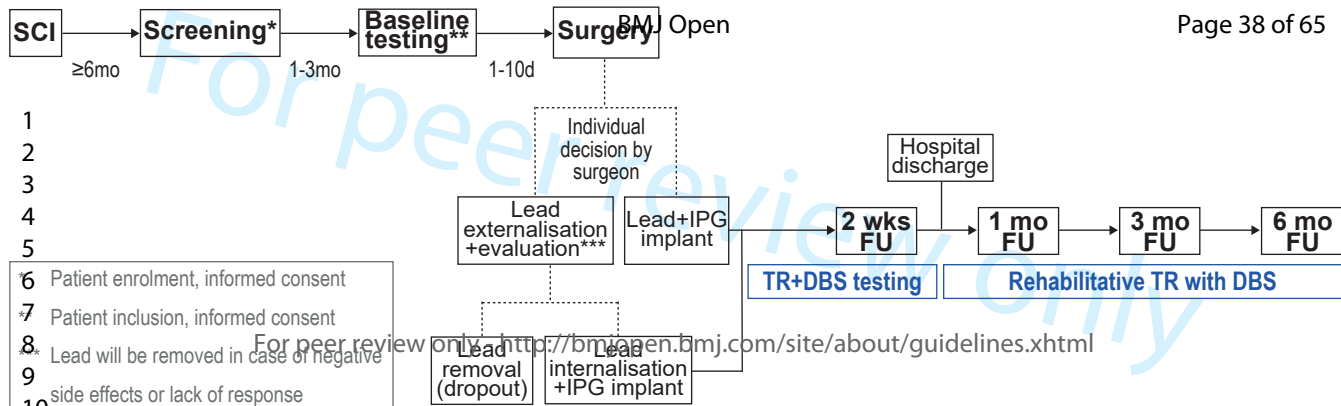
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- 1 Unilateral activation of the MLR with DBS
- 2 Spared fibres of the spinal cord bypass the lesion and transfer the signal
- 3 Activation of CPGs below the injury initiates locomotion



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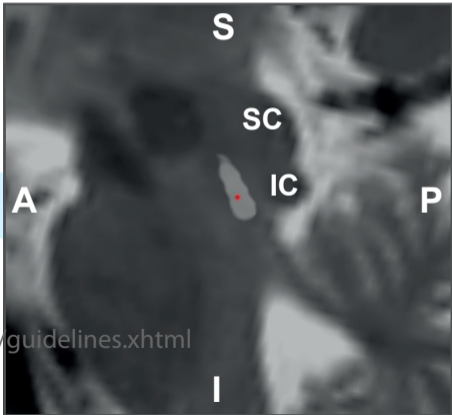
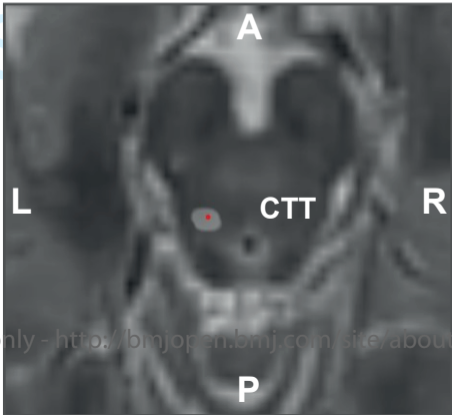
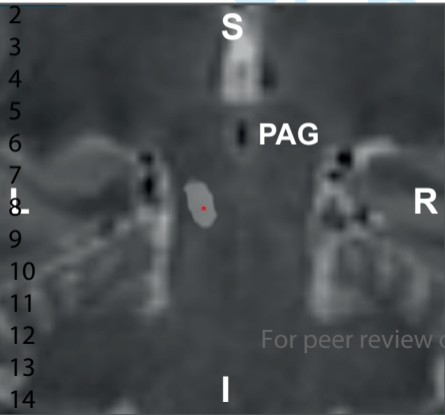
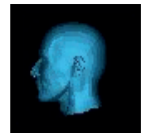
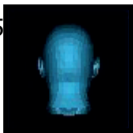
\*6 Patient enrolment, informed consent  
 \*7 Patient inclusion, informed consent  
 \*\*8 Lead will be removed in case of negative  
 9 side effects or lack of response  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym  <i>A phase I/II open-label multicenter trial to evaluate safety and preliminary efficacy of unilateral deep brain stimulation of the mesencephalic locomotor region in patients with incomplete spinal cord injury (DBS-SCI).</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry  <i>Registered on <a href="http://clinicaltrials.gov">clinicaltrials.gov</a> (NCT03053791, DBS-SCI).</i>
	2b	All items from the World Health Organization Trial Registration Data Set  <i>See <a href="http://ClinicalTrials">ClinicalTrials</a> registry and full study protocol.</i>
Protocol version	3	Date and version identifier  <i>Latest approved (Ethical Committee of the Canton of Zurich) study version: version 5, 12.09.2019.</i>

## Funding

## 4 Sources and types of financial, material, and other support

*Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich. No specific research grant has been declared for this study. The funding sources had no influence on the design of this study and the writing of this manuscript, and will not have any influence on study execution, data analysis, data interpretation, or decision to publish results.*

1  
2 Roles and  
3 responsibilities

5a Names, affiliations, and roles of protocol contributors

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LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis.

1  
2 5b Name and contact information for the trial sponsor  
3

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6 *University Hospital Zurich*

7 *Frauenklinikstrasse 10*

8 *8091 Zurich, Switzerland*

9 *Tel: +41-(0)44-255 2660*

10 *Fax: +41-(0)44-255 4505*

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16 5c Role of study sponsor and funders, if any, in study design; collection,  
17 management, analysis, and interpretation of data; writing of the report;  
18 and the decision to submit the report for publication, including whether  
19 they will have ultimate authority over any of these activities  
20

21 *The funding source had no role in the design of this study and will not*  
22 *have any role during its execution, analyses, interpretation of the data,*  
23 *or decision to submit results. The authors have no competing interests*  
24 *to declare.*  
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30 5d Composition, roles, and responsibilities of the coordinating centre,  
31 steering committee, endpoint adjudication committee, data  
32 management team, and other individuals or groups overseeing the  
33 trial, if applicable (see Item 21a for data monitoring committee)  
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## Introduction

### Background and rationale

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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

*Briefly: A spinal cord injury (SCI) is a devastating event with an immediate impact on an individual's health and quality of life. Even though most spinal cord injuries are clinically incomplete, major neurological and functional recovery plateaus after three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of CNS targets, e.g. electrical spinal cord stimulation or deep brain stimulation, has aroused scientific interest in recent years with some encouraging results. In deep brain stimulation (DBS) the mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command center that controls the initiation and maintenance of locomotion, is considered a promising target. Animal experiments have shown that MLR-DBS can acutely induce swimming and walking in rats with spinal white matter destructions of >85%. Promising pre-clinical data and the minimally-invasive nature of DBS have led to the initiation of this study to investigate the therapeutic potential of MLR-DBS to improve recovery of gait in a small cohort of patients.*

6b

*The study comprises no comparators, performance will be compared between different timepoints. The presence of an SCI will be documented by neuroimaging and the risk of paraplegia resulting from other origins can be excluded. Therefore, a mere placebo-effect resulting in improvement of the ability to walk is extremely unlikely. A control group undergoing sham-surgeries is not necessary at this early stage of research on this topic.*

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- Objectives 7 Specific objectives or hypotheses
- We hypothesize that MLR-DBS can modulate spared fibers of the reticulospinal tract system that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking. We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.*
- 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, noninferiority, exploratory)
- Briefly: The DBS-SCI trial is a prospective one-armed multi-centre study. The trial is considered successful if the patient's performance in the 6 minutes walking test (6MWT, primary outcome measure) 6 months after treatment start is at least 30% better compared to performance at baseline.*

## 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

*Briefly: The trial is conducted and data are collected at two sites in Zurich, Switzerland: the University Hospital Zurich (Departments of Neurosurgery and Neurology, both specialized in deep brain stimulation), and the Spinal Cord Injury Center of the Balgrist University Hospital (specialized in the management of acute and chronic SCI including neurorehabilitation). The study is open to national and international patients, however, basic understanding of German or English is required.*



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2 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility  
3 criteria for study centres and individuals who will perform the  
4 interventions (eg, surgeons, psychotherapists)

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6 *Addressed in "Inclusion and exclusion criteria" section of manuscript.*

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8 *Inclusion criteria:*

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- *Informed consent*
  - *Participation in two assessment sessions before enrolment*
  - *Willingness and ability to comply with the protocol and to attend all required study training and visits*
  - *Female or male*
  - *Age 18-75*
  - *Motor incomplete SCI*
  - *Level of lesion at or above T10, based on AIS level, preservation of sacral function*
  - *Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition*
  - *Minimum 6 months of recovery after SCI*
  - *Completed in-patient rehabilitation program*
  - *WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters*
  - *Stable medical and physical condition*
  - *Adequate care-giver support and access to appropriate medical care in patient's home community*

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*Exclusion criteria:*

- *Enrolment of the investigator, her/his family members, employees and other dependent persons*
- *Limitation of standing and walking function based on accompanying (CNS) disorders*
- *Cardiovascular disorders*
- *Implanted technical devices*
- *Significant autonomic dysreflexia*
- *Cognitive disorders/brain damage*
- *Drug refractory epilepsy*
- *Severe joint contractures disabling or restricting lower limb movements*
- *Haematological disorders with increased risk of bleeding*
- *Participation in another study with investigational drug within 30 days preceding and during the present study*
- *Congenital or acquired lower limb abnormalities*
- *Women who are pregnant or breast feeding or planning a pregnancy during the course of the study*
- *Lack of safe contraception*
- *Inability to follow the procedures of the study*
- *Known or suspected non-compliance, drug or alcohol abuse*
- *Current or prior malignancy*

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2 Interventions 11a Interventions for each group with sufficient detail to allow replication,  
3 including how and when they will be administered  
4  
5 *Interventions and assessments are described in detail in study*  
6 *protocol.*  
7  
8 *Briefly:*  
9  
10 *Intervention model: single group assignment (single group of patients*  
11 *with incomplete SCI), single armed study, all patients receive*  
12 *treatment.*  
13  
14 *Procedure:*  
15  
16 • *Implantation of a deep brain stimulation system (electrodes*  
17 *into the mesencephalic locomotor region and Medtronic Activa*  
18 *SC impulse generator into pectoral or abdominal region).*  
19  
20 • *Deep brain stimulation of mesencephalic locomotor region*  
21 *during rehabilitative training with regular follow-ups until 6*  
22 *months after implantation.*  
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- 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)

*Should a subject's participation in the investigation be discontinued, the reason for discontinuation, e.g. safety concerns, must be documented in the source documents. The Sponsor may terminate the study prematurely according to certain circumstances, for example: ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, or early evidence of benefit or harm of the experimental intervention. Participants may withdraw from participation at any time without need to give reasons. If the patient wishes so, the implanted DBS system will be surgically removed. The procedure will not be charged from the patient or his health insurance. The Investigator may decide to withdraw a subject from the investigation at any time. The investigators must make every effort to contact the subject to ascertain the reason for missed appointments if a subject does not return for follow-up assessments. Correspondence with the subject is necessary for regular withdrawal from pending follow-up.*


*The Study Protocol, Case Report Forms, Informed Consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Any change affecting the subject requires that the subject is informed about the change(s). An updated signed and dated informed consent shall be obtained from the investigator and the study participant, no later than during the subject's next follow-up visit under the scope of this investigation.*

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- 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

*Initially, all participants are informed in detail about the study, its background and goals, the importance of training intensity, and the importance of adherence to the study plan. At follow-ups, feedback sessions are performed and experience between participants and investigators is exchanged. Regular correspondence with the subjects additionally ensures adherence to intervention protocols. Subjects are asked to document their daily activities and training sessions, which is regularly reported to the investigators in order to monitor training frequency and intensity (in case of home training or training in an external rehab center). In addition, physical activity during training and daily life is monitored by wireless sensors mounted to the patient's wrists, ankles and wheelchair, and data are regularly transferred via SSL-encrypted links (https) established between sites (e.g. a patient's home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).*

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- 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

*Prior to surgery, all medication that has blood-thinning effect (effect on blood coagulation or platelet function, e.g. Aspirin, Plavix, Marcoumar, Valproic acid, Gingko) is prohibited. The patients are informed by the surgeon prior to surgery about these medications and how they should be discontinued. If there is an indication for continuous intake of an anticoagulant or antiplatelet drug, the patient has to be excluded from the study. Patients with implanted technical devices, e.g. cardiac pacemakers, are not eligible for study participation.*

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- 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
- Briefly, the primary outcome measure for improvement of ambulation in this study is the gain of covered distance in the 6 minutes walking test (6MWT) at 6 months post implantation compared to baseline level. Additionally, a variety of quantitative and qualitative secondary outcome measures are performed, e.g. kinematic assessments, electrophysiological measurements and questionnaire-based assessments.*
- 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)
- Briefly, patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later (with or without temporary lead externalisation). After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS. See Figure 3 of manuscript.*
- 

1  
2 Sample size 14 Estimated number of participants needed to achieve study objectives  
3 and how it was determined, including clinical and statistical  
4 assumptions supporting any sample size calculations  
5  
6 *Briefly, we aim to include 5 patients in the study who have to complete*  
7 *all preoperative and postoperative examinations until 6 months after*  
8 *surgery, resulting in a total of 11 timepoints. In case of withdrawal of*  
9 *participation or arising complications (dropouts and incomplete follow-*  
10 *up), we aim to include two more patients (replacement of*  
11 *dropouts/withdrawal). The number of subjects is based on the aim of*  
12 *gaining information on treatment effectiveness with adequate safety.*  
13 *Preliminary studies of PPN stimulation in patients with gait*  
14 *disturbance and falls due to Parkinson's disease have been analyzed*  
15 *in a retrospective review by Morita et al., 2014. Sample sizes ranged*  
16 *from 1 to 14 in 12 publications. We estimate a relative effect size of*  
17 *30% improvement in the 6MWT 6 months after treatment start*  
18 *compared to performance at baseline to be clinically relevant. A*  
19 *sample size of five patients provides us with a power (1- $\beta$ ) of 80% ( $\alpha =$*   
20 *0.05). We judge that the selected sample size, based on previous*  
21 *experience in deep brain stimulation of the MLR, will provide*  
22 *acceptable clinical validity for the study objectives.*  
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view only

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2 Recruitment 15 Strategies for achieving adequate participant enrolment to reach  
3 target sample size  
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5 *In summary, all candidate patients, namely patients able to stand with*  
6 *or without walking aid and with a stable neurological condition, are*  
7 *screened and have to meet all of the inclusion and none of the*  
8 *exclusion criteria. Subjects will undergo preoperative examinations*  
9 *(e.g. MRI scans of the head and spine, neuropsychological,*  
10 *psychiatric and sleep status assessments etc.) according to our*  
11 *standard protocols of DBS for movement disorders, based on*  
12 *certification criteria of highly-specialized-medical DBS centers in*  
13 *Switzerland. Neurological assessments for SCI related impairment as*  
14 *defined by the study protocol are performed at the Spinal Cord Injury*  
15 *Center of Balgrist University Hospital. The subject population enrolled*  
16 *in this investigation will be comprised of male and female patients*  
17 *from our out-patient clinic at Balgrist University Hospital or from*  
18 *international volunteers actively contacting the investigators based on*  
19 *information obtained from study registries. Patients who do not meet*  
20 *all in- and exclusion criteria are not eligible to participate in this*  
21 *investigation. There will be no specific gender distribution as gender*  
22 *specific differences concerning efficacy and safety of the*  
23 *investigational diagnostic process are not to be expected.*  
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### 37 **Methods: Assignment of interventions (for controlled trials)**

#### 38 Allocation:

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41 Sequence 16a Method of generating the allocation sequence (eg, computer-  
42 generation generated random numbers), and list of any factors for stratification.  
43 To reduce predictability of a random sequence, details of any planned  
44 restriction (eg, blocking) should be provided in a separate document  
45 that is unavailable to those who enrol participants or assign  
46 interventions  
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51 Allocation 16b Mechanism of implementing the allocation sequence (eg, central  
52 concealment telephone; sequentially numbered, opaque, sealed envelopes),  
53 mechanism describing any steps to conceal the sequence until interventions are  
54 assigned  
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2	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
3			and who will assign participants to interventions
4			
5			N/A
6			
7	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
8	(masking)		participants, care providers, outcome assessors, data analysts), and
9			how
10			
11			N/A
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13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
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Or peer review only



## Methods: Data collection, management, and analysis

Data collection methods 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

*Addressed in “Study design”, “Clinical assessments”, and “Electrophysiological assessments” sections, and Table 2 and Table 3 of manuscript.*

*The primary outcome measure (6-minute walking test) is an internationally recognized test to assess walking capacity in spinal cord injured patients, widely used in clinical trials and clinical routine. During the 6MWT, the patient is accompanied by an experienced investigator (physiotherapist).*

*Using a variety of standardized, well-known and widely used quantitative, qualitative and questionnaire-based methods as secondary outcome measures, the study additionally collects a big data set on motor, sensory, autonomic function and quality of life. For example, the WISCI (Walking Index for Spinal Cord Injury) is frequently used in clinical trials to assess walking function on an ordinal scale, and it captures the extent and nature of assistance a person with SCI requires to walk. To address the burden of neurogenic lower urinary tract dysfunction on patient’s quality of life after SCI and to analyse the effect of MLR-DBS on recovery of lower urinary tract function, a combination of qualitative (bladder diary, validated questionnaire Qualiveen) and quantitative assessments (urodynamic measurements, renal ultrasound) of bladder function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.*

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- 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

*Regular correspondence with the subjects in addition to regular follow-ups promotes retention and adherence to intervention protocols. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material. In case of complete implant removal, the patients will receive a short-term follow-up after 4 to 6 weeks by the surgeon to assess wound-healing and outcome of surgery. Afterwards, the clinical follow-up for SCI will be performed at the Balgrist University Hospital according to clinical standards. In case the patient withdraws from the study but refuses removal of the implants, clinical follow-up will be performed as well at the Department of Neurosurgery, University Hospital of Zurich, and at the Balgrist University Hospital according to clinical standards. In case of withdrawal, the patient's study related data will remain in the study.*

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

*Data management system: All data will be entered in a case report form (CRF). Every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors. Overall, the PI is responsible for data handling. The PI and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Investigational data shall be analyzed by the PI and may be transferred to a location outside of Switzerland and/or any other regulatory authority. All data from the CRFs will be transferred to an electronic database by the study coordinator at USZ. All paper CRFs and other documents will be scanned and stored as PDF files. Data transfer will be overseen and double-checked by the PI personally to prevent copy failures.*

*Data security, access and backup: According to corresponding national laws the patient must declare in writing that he or she agrees to the recording of his or her medical data, respectively, and if necessary, the reporting to national health authorities. The CRF and submitted source data are archived by the data owner (PI) for at least 15 years as required by national law. The investigator keeps originals of all source data and an original dated and signed duplicate of the patient consent form of each patient together with other essential study documents at the study center in accordance with the national law. The electronic database and scans of paper CRFs and documents will serve as backup and vice versa.*

*Electronic and central data validation: The investigator confirms with his or her signature on the CRF that all statements and data are complete and correct. All incoming CRF are checked for plausibility and completeness. If necessary, the investigator/study nurse will add missing data or correct inconsistent statements. Any change or correction to data reported on a CRF shall be tracked. Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the CRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall be explained in writing.*

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Statistical methods

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

*Statistics will be restricted to descriptive statistics. The trial is considered successful if the patient's performance in the 6MWT has improved by at least 30% at 6 months after treatment start compared to baseline (two-samples t-test).*

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

N/A

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)

N/A

**Methods: Monitoring**

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2 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role  
3 and reporting structure; statement of whether it is independent from  
4 the sponsor and competing interests; and reference to where further  
5 details about its charter can be found, if not in the protocol.  
6 Alternatively, an explanation of why a DMC is not needed  
7  
8 *Monitoring visits at the investigator's site prior to the start and during*  
9 *the course of the study will help to follow up the progress of the*  
10 *clinical study, to assure utmost accuracy of the data and to detect*  
11 *possible errors at an early time point. The Sponsor-Investigator*  
12 *organizes professional independent monitoring for the study. All*  
13 *original data including all patient files, progress notes and copies of*  
14 *laboratory and medical test results will be available for monitoring.*  
15 *The monitor will review all or a part of the CRF/eCRFs and written*  
16 *informed consents. The accuracy of the data will be verified by*  
17 *reviewing the above referenced documents. The investigator's site will*  
18 *collaborate with the Clinical Trials Center (CTC) of the University*  
19 *Hospital Zurich to ensure monitoring. A study specific monitoring plan,*  
20 *developed according to the CTC's SOP on monitoring activities,*  
21 *regulates extent, frequency and nature of monitoring activities.*  
22 *A quality assurance audit/inspection of this study may be conducted*  
23 *by the cantonal ethical committee (CEC) and by Swissmedic. The*  
24 *quality assurance auditor/inspector will have access to all medical*  
25 *records, the investigator's study related files and correspondence, and*  
26 *the informed consent documentation that is relevant to this clinical*  
27 *study. The investigator will allow the persons being responsible for the*  
28 *audit or the inspection to have access to the source data/documents*  
29 *and will answer any questions arising. All involved parties will keep*  
30 *the patient data strictly confidential.*  
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46 21b Description of any interim analyses and stopping guidelines, including  
47 who will have access to these interim results and make the final  
48 decision to terminate the trial  
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50 *N/A. The regulatory authorities receive an annual safety and interim*  
51 *report.*  
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- 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
- Every abnormal finding that appears for the first time or worsens during the course of the study will be recorded on the CRF and reported as adverse event. Adverse events (e.g. wound infections) will be interrogated for at each contact between the responsible investigator and the study subject. All pathological and clinically relevant findings in physical and neurological examinations, vital signs, clinical chemistry, hematology, and during surgery will be documented as adverse events. Complications related to assessments (e.g. falls during walking tests) will be reported as adverse events.*
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
- A quality assurance audit of this study may be conducted by the cantonal ethical committee and by Swissmedic. The quality assurance auditor will be independent from the investigators and sponsor, and have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will grant the auditor access to the source data/documents and will answer any questions arising during the audit. All involved parties will keep patient data strictly confidential.*

## Ethics and dissemination

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
- Ethical approval has already been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in 2017. Latest approved protocol version: version 5, 12.09.2019.*
- 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)
- Amendments are sent to and evaluated by the Cantonal Ethical Committee and Swissmedic. Substantial amendments are only implemented after approval by the Cantonal Ethical Committee and Swissmedic, respectively. Any change affecting the study participants requires that the subject is informed about the change(s). An updated signed and dated informed consent will be obtained from the subject by the investigator, no later than during the subject's next follow-up visit under the scope of this investigation.*
- As addressed in the "Discussion" section of the manuscript, an amendment to the study protocol is currently being written in order to include patients already 3 months after injury (instead of 6).*

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- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
- Before inclusion of a patient, the potential participant is informed by the investigator about the nature and purpose of the trial, the procedures involved, expected duration, potential risks and benefits, and any discomfort that might occur. Each participant will be informed that the participation is voluntary and that he/she may withdraw consent from the study at any time. Withdrawal of consent will not affect the patient's subsequent medical assistance and treatment. The participant is informed that his/her medical records may be examined by authorized individuals other than their treating physician. All participants are provided with a participant information sheet and a consent form describing the study and providing sufficient information for patients to make an informed decision about their participation in the study. Sufficient time will be given to the participant to decide whether to participate or not. Depending on the date of screening, the time frame is 20-80 days before hospitalization. The patient information sheet and the consent form have been reviewed and approved by the Cantonal Ethical Committee and Swissmedic. The formal consent of a participant is obtained before the participant undergoes any study procedure. The participant has to read and consider the statement before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is also signed and dated by the investigator (or his designee), and will be retained as part of the study records.*
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
- N/A



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2 Confidentiality 27 How personal information about potential and enrolled participants will  
3 be collected, shared, and maintained in order to protect confidentiality  
4 before, during, and after the trial  
5  
6 *All data will be entered in a database as recorded in the CRF and*  
7 *every patient will receive an anonymized and unique patient identifier.*  
8 *The investigator will compile a confidential list, which relates these*  
9 *patient numbers to the patient's personal information. This separately*  
10 *stored list will only be accessible to the study team and the monitor.*  
11 *Original patient files may be viewed by monitors, auditors and*  
12 *inspectors.*  
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18 Declaration of 28 Financial and other competing interests for principal investigators for  
19 interests the overall trial and each study site  
20  
21 *The authors have no conflicts of interest to declare. Investigators and*  
22 *collaborators receive no financial or other compensation for work*  
23 *rendered in accordance with the study, despite their regular income*  
24 *from their respective affiliations.*  
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28 Access to data 29 Statement of who will have access to the final trial dataset, and  
29 disclosure of contractual agreements that limit such access for  
30 investigators  
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32 *After termination of the study, study data will be available for analysis*  
33 *only for persons or institutes assigned by the PI, according to local*  
34 *regulations. Direct access to source documents will be permitted for*  
35 *purposes of monitoring, audits and inspections.*  
36  
37 *The PI maintains all essential clinical investigation documents from*  
38 *prior, during and after the clinical investigation on file at the site.*  
39 *Originals of all study-related report forms, administrative documents,*  
40 *medical records, and a list allowing patient identification will be stored*  
41 *in the study headquarters University Hospital Zurich and Balgrist*  
42 *University Hospital for at least 15 years after completion of the trial.*  
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- 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
- Any damage developed in relation to study participation is covered by the study's insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the PI (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly in the event of health problems or other injuries sustained during or after the course of study. The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential. The patient and his health insurance will not be charged for screening, treatment and follow-up (until 6 months after surgery), but there will be no compensation for participation in the study. Clinical examinations and treatments after completion of the 6 months' follow-up will be charged from the patient's health insurance.*
- Dissemination policy 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
- The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international conferences. Results will be communicated to participants in layman's terms.*

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- 31b Authorship eligibility guidelines and any intended use of professional writers
- Publication(s) and/or presentation(s) of the study results is encouraged. Neither the sponsor nor the investigators have the right to prevent publication, except for patent or copyright reasons. Staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors, if applicable. A copy of all publications will be sent to the coauthors. The PI will decide about authorship and the sequence of co-authors, including the last author, based on the amount and importance of the contribution to the study as judged by the PI. No professional writers will be used.*
- 31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
- N/A

## Appendices

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| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates   |
|                            |    | <i>Please see Appendix 1.</i>  |
| 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  |

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

Appendix 1 - Model consent form

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For peer review only


**Informed consent for participation in a clinical study**

- Please read this document carefully
- Please ask in case of questions or further interest.

<b>Study identifier:</b> (of the local ethics committee)	BASEC 2016_01104
<b>Study title:</b>	Deep Brain Stimulation in patients with incomplete spinal cord injury for improvement of gait Tiefe Hirnstimulation zur Verbesserung des Gehens bei Patienten mit Rückenmarksverletzungen
<b>Responsible institution (Sponsor)</b> (complete address):	Neurochirurgische Klinik, UniversitätsSpital Zürich, Frauenklinikstrasse 10, CH-8091 Zürich
<b>Study site:</b>	UniversitätsSpital Zürich and Uniklinik Balgrist Zürich
<b>Principal investigator:</b> Name, First name:	Lennart Stieglitz MD, Chief of service, Specialist for Neuromodulation Armin Curt MD, Chairman Center for Paraplegia
<b>Participant:</b> Name and first name, date of birth	<input type="checkbox"/> female <input type="checkbox"/> male

- I was informed in detail orally as well as in written form about the purpose, the conduction, about expected effects, possible side-effects, risks and benefits of the study by the signing surgeon.
- My questions concerning my participation in the study were answered satisfyingly. I received the study information of 07.06.2019 Version 2 (two parts) and receive a copy of this informed consent form. I accept the content of the above mentioned study information.
- I participate in this study voluntarily. I can withdraw from participation at any time and will not suffer disadvantages concerning my ongoing medical treatment hence.
- I was informed about other possible treatment options.
- I was given enough time to decide about my participation.
- I was informed, that an insurance company will cover damages resulting from participation in the study, in case I can prove the connection clearly.
- I agree that my general practitioner is informed about my participation in the study: Yes  No .
- In case of incidental findings I want to a)  be informed unconditionally; b)  not informed or c)  I want to leave the decision with the following person: .....
- I know, that my personal data may only be used in coded form for scientific purposes. I agree, that the responsible specialists of the initiator of the study and the local authorities (cantonal ethics committee) may be granted insight into the original data for control purposes, but only under strict compliance with confidentiality.
- I am aware, that the obligations mentioned in the study information are to be obliged during the study. The principal investigator may exclude me from the study at any time with my best interests in mind.

Place, date	Signature study participant
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**Confirmation of the investigator: Hereby I confirm that I informed the participant in detail about the character, importance and relevance of the study.** I will fulfill all legal obligations in connection with this study. Should I learn of aspects that could affect the willingness of the participant to participate during the course of the study, I will inform him/her immediately.

Ort, Datum	Signature of the investigator
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# BMJ Open

## Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-SCI) – protocol of a prospective one-armed multi-centre study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047670.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Aug-2021
Complete List of Authors:	Stieglitz, Lennart; University Hospital Zurich, Department of Neurosurgery Hofer, Anna-Sophie; University Hospital Zurich, Department of Neurosurgery; University of Zurich Institute for Regenerative Medicine Bolliger, Marc; Balgrist University Hospital, Spinal Cord Injury Center Oertel, Markus; University Hospital Zurich, Department of Neurosurgery Filli, Linard; Balgrist University Hospital, Spinal Cord Injury Center Willi, Romina; Balgrist University Hospital, Spinal Cord Injury Center Cathomen, Adrian; Balgrist University Hospital, Spinal Cord Injury Center Meyer, Christian; Balgrist University Hospital, Spinal Cord Injury Center Schubert, Martin; Balgrist University Hospital, Spinal Cord Injury Center Hubli, Michèle ; Balgrist University Hospital, Spinal Cord Injury Center Kessler, Thomas; Balgrist University Hospital, Department of Neuro-Urology Baumann, Christian; University Hospital Zurich, Department of Neurology Imbach, Lukas; University Hospital Zurich, Department of Neurology Krüsi, Iris; Balgrist University Hospital, Spinal Cord Injury Center Prusse, Andrea; Balgrist University Hospital, Spinal Cord Injury Center Schwab, Martin; University of Zurich Institute for Regenerative Medicine Regli, Luca; University Hospital Zurich, Department of Neurosurgery Curt, Armin; Balgrist University Hospital, Spinal Cord Injury Center
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, Neurological injury < NEUROLOGY, Spine < ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, Clinical trials < THERAPEUTICS

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3 1 Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-  
4 SCI) – protocol of a prospective one-armed multi-centre study  
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Word count: 5422 words

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3 37 **ABSTRACT**  
4

5 38 **Introduction:** Spinal cord injury (SCI) is a devastating condition with immediate impact on the  
6 individual's health and quality of life. Major functional recovery reaches a plateau three to four  
7 39 months after injury despite intensive rehabilitative training. To enhance training efficacy and  
8 40 improve long-term outcomes, the combination of rehabilitation with electrical modulation of the  
9 41 spinal cord and brain has recently aroused scientific interest with encouraging results. The  
10 42 mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor  
11 43 command and control centre, is considered a promising target for deep brain stimulation (DBS)  
12 44 in patients with SCI. Experiments showed that MLR-DBS can induce locomotion in rats with  
13 45 spinal white matter destructions of >85%.  
14 46

15 47 **Methods and analysis:** In this prospective one-armed multi-centre study, we investigate the  
16 48 safety, feasibility, and therapeutic efficacy of MLR-DBS to enable and enhance locomotor  
17 49 training in severely affected, subchronic and chronic American Spinal Injury Association  
18 50 Impairment Scale C patients in order to improve functional recovery. Patients undergo an  
19 51 intensive training program with MLR-DBS while being regularly followed-up until 6 months  
20 52 post-implantation. The acquired data of each timepoint are compared to baseline while the  
21 53 primary endpoint is performance in the 6 Minute Walking Test (6MWT). The clinical trial  
22 54 protocol was written in accordance with the Standard Protocol Items: Recommendations for  
23 55 Interventional Trials checklist.  
24 56

25 57 **Ethics and dissemination:** This first in-man study investigates the therapeutic potential of  
26 58 MLR-DBS in SCI patients. One patient has already been implanted with electrodes and  
27 59 underwent MLR stimulation during locomotion. Based on the preliminary results which promise  
28 60 safety and feasibility, recruitment of further patients is currently ongoing. Ethical approval has  
29 61 been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-  
30 62 01104) and Swissmedic (10000316). Results will be published in peer-reviewed journals and  
31 63 presented at conferences.  
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33 65 **Trial registration:** Registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017.  
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40 72 **Keywords:** Spinal cord injury, deep brain stimulation, mesencephalic locomotor region,  
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## 72 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 73 • This prospective one-armed multi-centre proof-of-concept study investigates the safety,  
74 feasibility and therapeutic potential of MLR-DBS to improve walking function after  
75 severe incomplete SCI.
- 76 • Patients with completed in-patient rehabilitation with highly limited ambulatory capacity  
77 are screened and considered for study enrolment.
- 78 • The study comprises a variety of clinical and electrophysiological assessments before,  
79 during, and after electrode implantation.
- 80 • Patients undergo intensive rehabilitative training with MLR-DBS and are followed-up  
81 on a regular basis until 6 months post-implantation.
- 82 • The primary endpoint is improvement of locomotion measured by the 6MWT 6 months  
83 after electrode implantation compared to baseline performance.

84

## 85 INTRODUCTION

86 In the event of spinal cord injury (SCI) a person's life turns upside down within a split second,  
87 and a multitude of body functions are either severely impaired or completely lost instantly.  
88 Reacquiring lost functions including locomotion is of high importance for affected patients.[1]  
89 However, it remains a largely unmet medical need due to the lack of treatment options to  
90 sufficiently rewire interrupted fibre tracts and enhance repair of the damaged human spinal  
91 cord. Despite decades of basic research, neuro-rehabilitative training currently remains the  
92 only treatment option that increases the chances of long-term improvement of sensory-motor  
93 functions.[2,3] Even though most SCIs spare some descending and ascending fibre tracts,  
94 leaving the sublesional spinal cord [4] only incompletely disconnected from the brain, functional  
95 recovery remains limited in most cases.[3,5,6] The number of spared descending fibres is often  
96 insufficient to convey appropriate control signals to sublesional locomotor circuits, e.g. central  
97 pattern generators (CPGs), which are thus deprived of supraspinal input and modulation,[7]  
98 and fail to induce rhythmic motor patterns.[8,9] However, these local rhythm generators remain  
99 functional and can be reactivated, e.g. by direct electrical stimulation in combination with  
100 training.[10–12] To increase the efficiency and efficacy of neurorehabilitation, locomotor  
101 training has therefore been combined with electrical epidural and transcutaneous stimulation  
102 of the spinal cord in small cohorts of patients in recent years, yielding promising results.[3,13–  
103 15] Another encouraging approach to recruit inactive, yet intact, sublesional motor circuits  
104 involves the electrical activation of spared descending reticulospinal tract fibres (Figure 1).[16]  
105 The majority of reticulospinal fibres arise from the medial medullary reticular formation, which  
106 relays the output of its upstream target, the mesencephalic locomotor region (MLR),[17–19] to  
107 the spinal cord. The MLR is a phylogenetically conserved key locomotor control centre in the  
108 brainstem, and is comprised of two main nuclei, the pedunculopontine (PPN) and the  
109 cuneiform nucleus (CNF).[20–22] The PPN is associated with exploratory behaviour,[23] and  
110 deep brain stimulation (DBS) of the PPN in patients with Parkinson's disease can result in a  
111 reversal of freezing of gait.[24–27] On the other hand, the CNF is known to be a main control  
112 region for locomotion initiation, maintenance and speed regulation.[23,28,29] Recently, the  
113 MLR has gained scientific and clinical interest as target for DBS to improve deficient gait after  
114 SCI [16] and stroke [30] with the CNF being proposed as main therapeutic target in recent  
115 rodent studies.[23,28,29] Acute electrical activation of the rat MLR has been shown to enable  
116 close to physiological hindlimb movements during walking and swimming in a rodent model of  
117 chronic incomplete SCI resembling an American Spinal Injury Association Impairment Scale  
118 (AIS) D score in humans.[16] In animals with severely paralyzed hindlimbs (AIS A-C in  
119 humans) stroke movements re-appeared with gravity-support during swimming with MLR-  
120 DBS. In an acute rodent stroke model, MLR-DBS was able to improve walking speed and limb  
121 coordination.[30] DBS in humans is considered safe, reversible and minimally-invasive, and is

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3 122 being routinely and successfully applied in the treatment of various movement disorders [31–  
4 123 36] with great technical progress in recent years.[37–39] While DBS of the PPN in Parkinson’s  
5 124 disease has not only yielded clearly positive therapeutic effects,[40] the CNF might be a  
6 125 promising target for locomotion initiation.  
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9 126 Function and anatomy of the brainstem motor systems are highly conserved across  
10 127 mammalian species.[41] Due to their dispersed projection pattern throughout the spinal cord  
11 128 white matter,[42,43] reticulospinal fibres are likely to be partially spared after incomplete SCI  
12 129 in humans,[44] and are crucial for functional recovery after SCI.[45,46]

13 130 Encouraging results from animal studies [16,30,47] have led to the initiation of a first in-man  
14 131 study that investigates MLR-DBS enabled intensive rehabilitative training and its potential to  
15 132 enhance locomotion in non-ambulatory, subchronic and chronic SCI patients. The study  
16 133 protocol is presented in this article.

17 134 We hypothesize that MLR-DBS can modulate the activity of spared reticulospinal fibres that  
18 135 bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network  
19 136 that supports walking (Figure 2). We propose that enhancing excitability of sublesional spinal  
20 137 motor circuits increases training efficacy and promotes recovery of motor function in patients  
21 138 with incomplete, subchronic and chronic SCI.  
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## 139 **METHODS AND ANALYSIS**

### 140 **Study design**

141 This prospective one-armed phase I/II multi-centre study is being conducted as cooperation of  
142 the University of Zurich, the University Hospital Zurich and the Balgrist University Hospital  
143 Zurich. Patients are screened and selected by SCI specialists and physiotherapists at the  
144 Balgrist University Hospital. Incomplete SCI is confirmed based on clinical examinations,  
145 magnetic resonance imaging (MRI), and electrophysiological measurements, and each  
146 patient's established drug therapy is recorded. After patient inclusion and baseline  
147 examinations, a DBS lead is stereotactically unilaterally implanted into the cuneiform part of  
148 the MLR, followed by infraclavicular or abdominal implantation of an impulse generator (IPG,  
149 Figure 3). The side of lead placement is chosen based on the functional and anatomical lesion  
150 extent, with preference for the less severely affected side to transmit as much descending  
151 brainstem motor signal as possible beyond the lesion via the primarily uncrossed reticulospinal  
152 fibres. The patients are followed-up on a regular basis until 6 months post-implantation, and  
153 the acquired data of each timepoint are compared with baseline findings. The primary outcome  
154 measure for improvement of ambulation in this study is the difference in covered distance in  
155 the 6 Minute Walking Test (6MWT) at 6 months post-implantation compared to baseline level.  
156 The trial is considered successful if the patient's performance in the 6MWT 6 months after  
157 treatment start is at least 30% [48] higher compared to performance at baseline. For the design  
158 of the clinical trial protocol we followed the SPIRIT (Standard Protocol Items:  
159 Recommendations for Interventional Trials) checklist.[49]

### 160 **Study population**

161 Female and male patients (18-75 years) with completed in-patient rehabilitation and at least 6  
162 months of recovery after SCI are screened and considered for study enrolment. We aim at  
163 including 5 patients, who have to complete all preoperative and postoperative examinations  
164 until 6 months after electrode implantation, resulting in a total of 11 timepoints. In case of  
165 withdrawal of participation, dropouts and incomplete follow-up, we will include a maximum of  
166 2 additional patients (replacement of dropouts/withdrawal). The study is open to national and  
167 international patients. Basic understanding of German or English is required. Patients who  
168 prematurely withdraw from the study will be offered complete removal of all implanted material,  
169 and will be followed-up according to clinical standards. The patients' study related data will  
170 remain in the study.

### 171 **Inclusion and exclusion criteria**

172 To be eligible for the study, a participant must fulfil all inclusion criteria and none of the  
173 exclusion criteria (Table 1).

174 **Table 1 – Inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
Informed consent	Enrolment of the investigator, her/his family members, employees and other dependent persons
Participation in two assessment sessions before enrolment (screening and baseline)	Limitation of standing and walking function based on accompanying (CNS) disorders
Willingness and ability to comply with the protocol and to attend required study training and visits	Cardiovascular disorders restricting physical training or peripheral nerve disorders
Female or male subject	Implanted technical devices (pacemaker, defibrillator, others)
Age 18-75	History of significant autonomic dysreflexia
Motor incomplete SCI	Cognitive disorders/brain damage
Level of lesion at or above T10, based on AIS level, preservation of sacral function	Drug refractory epilepsy
Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition (like haemorrhage, benign tumour)	Severe joint contractures disabling or restricting lower limb movements
Minimum 6 months of recovery after SCI	Haematological disorders with increased risk of bleeding during surgical interventions
Completed in-patient rehabilitation program	Participation in another study with investigational drug within 30 days preceding and during the present study
WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters	Congenital or acquired lower limb abnormalities (affection of joints and bone)
Stable medical and physical condition	Women who are pregnant or breast feeding or planning a pregnancy during the course of the study
Adequate care-giver support and access to appropriate medical care in patient's home community	Lack of safe contraception
	Inability of the participant to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc.
	Known or suspected non-compliance, drug or alcohol abuse
	Current or prior malignancy

175 CNS = central nervous system. SCI = spinal cord injury. AIS = ASIA (American Spinal Injury Association)

176 Impairment Scale. WISCI = Walking Index for Spinal Cord Injury. PI = principal investigator.

## 177 **Target area definition**

178 While the rodent CNF and its microstructure are nowadays well characterized,[23,28,29] the  
179 human CNF is poorly described, and presented only in a very limited number of stereotactic  
180 atlases. However, due to the high phylogenetic conservation,[41] the CNF can be defined by  
181 surrounding landmarks and coordinates available from lead implantation into the PPN and  
182 rodent stereotactic atlases (Figure 4).

## 183 **Surgery**

184 All individuals included in the study undergo unilateral stereotactic implantation of an  
185 intracranial lead (model 3389-28; Medtronic, Minneapolis, MN, USA) via a unilateral burrhole  
186 under local anaesthesia. The distal end of the DBS lead features narrow (0.5 mm) spacing  
187 between each of the four stimulation contacts of 1.5 mm length each. After mounting of the  
188 stereotactic frame, high resolution cranial computed tomography (CT) scans are performed  
189 and fused with the individual's MRI scan to retrieve stereotactic coordinates based on the pre-  
190 planned trajectory. Depending on the patient's preferences and the surgeon's decision,  
191 patients either receive a full implant consisting of a DBS lead, an extension and an IPG within  
192 one surgical session, or receive a lead only, which is externalized for maximal 10 days for  
193 evaluation of side effects and responsiveness to stimulation. In the latter scenario, the patient  
194 undergoes a second surgery with either removal of the lead (dropout of the study participant)  
195 or completion of the DBS system. For completion, the lead is connected to a Medtronic Activa  
196 SC model 37603 IPG using a Medtronic model 37086-60 or 37086-95 extension cable. The  
197 IPG is implanted subcutaneously in the pectoral or abdominal region, respectively, depending  
198 on the patient's physiognomy and preference.

199 Intraoperatively, at first electrophysiological mapping of the CNF is performed. Microelectrodes  
200 are precisely inserted along a predefined trajectory aiming towards the CNF with the Neuro  
201 Omega neuromodulation system and manual drive (Alpha Omega Engineering, Nazareth,  
202 Israel) attached to the stereotactic device. During electrode insertion (0.5 mm steps),  
203 microelectrode recordings (30 s at each position) of single and multi-unit activity (local field  
204 potentials, LFPs) are performed during resting state, imagination of walking, passive and active  
205 lower limb movement within 10 mm prior and maximum 5 mm after the projected target point.  
206 Signals are band pass filtered (1-500 Hz). Depending on the patient's anatomy up to five  
207 microelectrodes can be inserted simultaneously, in case of a presumed elevated risk of  
208 haemorrhage, the surgeon can decide to exclusively use macroelectrodes instead of  
209 microelectrodes. The centre of the region showing neuronal responsiveness to walking  
210 imagination, passive and active lower movement is subsequently stimulated while the patient  
211 performs a selection of motor tasks with the lower limbs hanging off the surgery table,  
212 accompanied by simultaneous electromyographic (EMG) recordings. Since this study is the



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3 213 first to investigate DBS of the CNF in human patients, no guidelines for optimal stimulation  
4 214 parameters are available. However, there is growing and comparable evidence from preclinical  
5 215 studies in various animal models suggesting low frequency stimulations ( $\leq 50$  Hz) at medium  
6 216 to broad pulse widths (200-1000  $\mu$ s) [16,50,51] which is likely to be transferable to humans  
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8 217 due to the evolutionarily conserved nature of the mesencephalic locomotor region across  
9 218 mammalian species. We thus initially stimulate with 20 Hz and 400  $\mu$ s pulse width at increasing  
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11 219 voltages, and frequency and pulse widths are then adjusted based on the individuals'  
12 220 intraoperative behavioural response. Up to three different parameter settings of fixed  
13 221 frequency and pulse width with varying voltages are extensively tested intraoperatively.  
14 222 Stimulation amplitude is slowly increased, and changes in range of motion with and without  
15 223 stimulation are measured by goniometers attached to knee and ankle while the patient  
16 224 performs rhythmic knee and ankle flexion/extension movements. Furthermore, speech and  
17 225 cognition are tested with and without stimulation, and the appearance of side effects, in  
18 226 particular pain sensations and paraesthesia, is closely monitored and documented. Additional  
19 227 electrophysiological measurements, including motor evoked potentials (MEPs) and  
20 228 somatosensory evoked potentials (SSEPs), are performed for neuromonitoring, and event (i.e.  
21 229 lower extremity motor response) related potentials (ERPs) are analysed. Ultimately, the  
22 230 coordinates resulting in best motor performance (e.g. greatest range of motion of knee joint,  
23 231 highest frequency of rhythmic knee flexions/extensions) at the lowest stimulation parameters  
24 232 without provoking side effects are chosen, and the quadripolar DBS lead is implanted with  
25 233 contact 2 located within the centre of the identified area, fixed to the skull, and either  
26 234 temporarily externalized or connected to an extension and IPG. All subjects subsequently  
27 235 receive a postoperative cranial CT scan to verify correct lead position and exclude surgery-  
28 236 associated complications (e.g. haemorrhages). Each patient recovers from surgery in the  
29 237 intermediate care unit overnight.

### 238 **Clinical assessments**

#### 239 6 Minute Walking Test (6MWT)

240 During the 6MWT,[48] the patient is asked to cover a maximal distance within 6 minutes on  
241 even ground without any obstacles. The patient is accompanied by an experienced investigator  
242 (i.e. physiotherapist) to prevent falling, and may rest at his own discretion and use a walking  
243 aid (consistent across all timepoints). The distance covered (m), time and number of rests  
244 (min, count) is documented. Each assessment is video recorded.

#### 245 10 Meter Walking Test (10MWT)

246 The 10MWT [52] is a widely used assessment tool to measure maximal walking speed (m/s).  
247 The patient is instructed to walk 10 m as quickly as possible, but safely, and is given 5 m for

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3 248 acceleration and deceleration. Patients may use assistive devices (consistent across all  
4 249 timepoints).

#### 7 250 Timed-Up and Go Test (TUG)

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9 251 The TUG is a basic evaluation tool of functional mobility. It measures the time (s) needed to  
10 252 rise from a chair, walk 3 m, turn around and return to a seated position. Participants are asked  
11 253 to perform the TUG at their self-selected normal speed, using their walking aid if required. The  
12 254 timer is started on the command “ready–set–go” and stopped as the patient returns to a seated  
13 255 position.

#### 17 256 Kinematic assessment

18 257 Kinematic assessments are performed during over-ground and treadmill walking. Individuals  
19 258 are secured using the FLOAT (“Free Levitation for Overground Active Training”),[53,54] a  
20 259 multidirectional overhead support system that allows patients to move in a large workspace  
21 260 that is equipped with a 3D motion capture system with infrared cameras (Vicon Motion Systems  
22 261 Ltd., Oxford, UK). The cameras are able to detect the position of reflective markers placed on  
23 262 patients’ anatomical landmarks, allowing the quantification of kinematic movement  
24 263 characteristics.[55,56] Additionally, muscle activity is measured with an EMG setup (myon AG,  
25 264 Schwarzenberg, Switzerland). These measures allow the quantification of patients’ walking  
26 265 function with high precision and the comparison of gait patterns within (with and without DBS)  
27 266 and between different sessions. In addition to walking assessments, maximal knee and ankle  
28 267 range of motion is evaluated with and without stimulation with the motion capture system during  
29 268 rhythmic flexion/extension tasks performed by the patient in supine or sitting position. Besides  
30 269 quantitative assessment of locomotor function, the FLOAT allows patients to train diverse  
31 270 activities such as level walking, running, stair manoeuvres, chair interactions or walking on  
32 271 uneven terrain with and without stimulation at the limit of their abilities with tailored body weight  
33 272 support.

#### 45 273 Long-term Monitoring of Physical Activity

46 274 For constant monitoring of physical activity during training and daily life, wearable, wireless  
47 275 sensors (<http://zurichmove.com/>) are mounted to the patient’s wrists, ankles, and wheelchair.  
48 276 Data are transferred via SSL-encrypted links (https) established between sites (e.g. a patient’s  
49 277 home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

#### 54 278 ASIA Impairment Scale (AIS)

55 279 The American Spinal Injury Association (ASIA) International Standards for Neurological  
56 280 Classification of SCI (ISNCSCI) [57] is an internationally used gold standard method of  
57 281 assessing the neurological status of an individual with SCI. The AIS is carried out by trained

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3 282 medical staff using the ISNCSCI worksheet (<https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/>).

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7 284 Modified Ashworth Scale (MAS)

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9 285 The MAS [58] is a clinical scale used to assess muscle spasticity in patients with lesions of the  
10 286 central nervous system. It is the most commonly used tool to evaluate changes of muscle tone  
11 287 in response to therapeutic interventions, e.g. anti-spasticity medication. Here, we aim to  
12 288 investigate the effects of MLR-DBS by itself on muscle tone and thus do not routinely modify  
13 289 each patient's established anti-spasticity treatment unless medically indicated. However,  
14 290 potential drug-stimulation interactions are considered in data interpretation.

15 289  
16 290  
17 291 Spinal Cord Independence Measure (SCIM III)

18 291  
19 292 The SCIM is a reference tool for the assessment of overall functional ability after SCI. The last  
20 293 version (III) of SCIM contains 19 tasks organized into 3 subscales: Self-care, Respiration &  
21 294 sphincter management, and Mobility.[59] The combined scores on all 19 tasks result in an  
22 295 overall score ranging from 0 to 100, with higher scores reflecting greater functional ability.

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25 296 Walking Index for Spinal Cord Injury (WISCI II)

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27 297 The WISCI assesses walking function on an ordinal scale,[60] and captures the extent and  
28 298 nature of assistance a person with SCI requires to walk. Rating is performed according to  
29 299 Ditunno et al.[60]

30 299  
31 300 Assessment of lower urinary tract (LUT) function

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33 301 To address the burden of neurogenic LUT dysfunction on patient's quality of life after SCI and  
34 302 to analyse the effect of MLR-DBS on recovery of LUT function, a combination of qualitative  
35 303 (bladder diary, QUALIVEEN questionnaire) and quantitative assessments (urodynamic  
36 304 measurements, renal ultrasound) of LUT function are applied in accordance to the European  
37 305 Association of Urology (EAU) Guidelines on Neuro-Urology.[61,62]

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3 313 for “Limitations”, “Constraints”, “Fears” and “Feelings”, and the calculated arithmetic  
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6 314 mean is transformed into values of 0-100.

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8 315 • Urodynamic assessments: Cystometry, uroflowmetry, pressure-flow studies,  
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10 316 electromyography and video-urodynamics provide objective information on functioning  
11 317 of the LUT and pelvic floor. Parameters retrieved are: cystometric capacity (mL),  
12 318 compliance (mL/cmH<sub>2</sub>O), detrusor overactivity (y/n), bladder volume at detrusor  
13 319 overactivity (mL), maximum detrusor pressure amplitude (cmH<sub>2</sub>O) during storage  
14 320 phase, urinary incontinence, maximum detrusor pressure (cmH<sub>2</sub>O) during voiding  
15 321 phase, detrusor pressure at maximum flow rate (cmH<sub>2</sub>O), maximum flow rate (mL/s),  
16 322 voided volume (mL), post-void residual (y/n and mL), pelvic floor electromyographic  
17 323 activity (normal/abnormal), vesico-uretero-renal reflux (y/n).  
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19 324 • Renal and bladder ultrasound: indirect assessment of LUT function, e.g. via post-void  
20 325 residual volume, detrusor thickness or distension of the renal pelvis or ureter.  
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## 26 326 Assessment of sexual function

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28 327 The Female Sexual Function Index (FSFI) [65,66] is gold standard for the evaluation of female  
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30 328 sexual function in clinical trials. It is questionnaire-based and contains 19-items including  
31 329 sexual arousal, orgasm, satisfaction and pain (score 2-80). The International Index of Erectile  
32 330 Function (IIEF) [67] is a standardized 15-item self-evaluation scale for male patients assessing  
33 331 erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and in  
34 332 general.  
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## 38 333 Epworth Sleepiness Scale (ESS)

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40 334 The ESS [68] measures a patient’s general level of daytime sleepiness. The patient rates the  
41 335 probability of falling asleep on a scale of increasing probability (0-3) for eight different  
42 336 situations.  
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## 46 337 Fatigue Severity Scale (FSS)

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48 338 The FSS [69] evaluates the impact of fatigue based on a short questionnaire containing nine  
49 339 statements rating the severity of fatigue symptoms.  
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## 52 340 Pain assessment

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54 341 The EMSCI (European Multicenter Study About Spinal Cord Injury) pain assessment form  
55 342 (EPAF) [70,71] and the Spinal Cord Injury Pain Instrument (SCIPI) [72–74] are standardized  
56 343 and validated tools to evaluate pain in individuals with SCI.  
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## 60 344 Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP)

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3 345 The GRASSP [75,76] is a standardized upper-limb impairment measure specifically used to  
4 346 assess recovery of upper limb function (strength, sensation, prehension) in individuals with  
5 347 complete or incomplete tetraplegia.

8 348 Short Form Health Survey to Assess Quality of Life (SF-36)

10 349 Patients with SCI experience tremendous changes in several aspects of everyday life and thus  
11 350 quality of life (QoL) [77] assessments are crucial in clinical trials. We employ the SF-36 [78], a  
12 351 multi-purpose, short-form health survey comprised of 36 questions that compares the relative  
13 352 burden of diseases and differentiates the health benefits produced by a wide range of different  
14 353 treatments. It yields an 8-scale profile of functional health and well-being scores,  
15 354 psychometrically based physical and mental health summary measures, and a preference-  
16 355 based health utility index. QoL is expressed as a score ranging from 0 to 100.

### 22 356 **Electrophysiological assessments**

24 357 Electrophysiological assessments are performed in addition to clinical examinations as they  
25 358 allow prediction of functional outcome and help objectify the extent of the spinal lesion, its  
26 359 stability and potentially recovery of specific functions after SCI.[79,80] Intraoperative  
27 360 somatosensory and motor evoked potentials are recorded for neuromonitoring purposes due  
28 361 to the close relationship of the CNF with surrounding brainstem structures.

33 362 Short-latency somatosensory evoked potentials (SSEPs)

35 363 SSEPs are performed to evaluate transmission of ascending signals within the dorsal column  
36 364 of the spinal cord and thus sensory function. The patient is in supine position, and stimulating  
37 365 electrodes are placed on the posterior tibial nerve (below the internal malleolus). Four  
38 366 subcutaneous recording electrodes are placed as follows: at L2 and L5, on the scalp (reference  
39 367 Fz and active Cz', 2 cm behind Cz), and a ground around the ankle. Cortical recording  
40 368 electrodes are positioned in accordance with the International 10–20 system.[81] Stimulation  
41 369 parameters are 200  $\mu$ s, up to 100 mA at a frequency of 3.1 Hz. The signal is recorded between  
42 370 30 and 300 Hz with 50 Hz notch filter. Waveforms are measured after 200-800 averages.  
43 371 Dorsal horn negativity (N24) is measured on the lumbar derivation (L5-L2) and represents  
44 372 peripheral conduction time. The post-Rolandic positivity (P45) is measured on the scalp  
45 373 derivation and represents the total conduction time. All measures are recorded before, during  
46 374 and after electrode implantation, and before and after first (week 1 after implantation) and last  
47 375 (6 months after implantation) 6MWT assessments. Response latency (ms) and amplitude ( $\mu$ V)  
48 376 are compared between timepoints and conditions (stim/no stim).

58 377 DBS evoked potentials (DBS-EPs)

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3 378 DBS-EP testing is performed similar to SSEP measurements. However, instead of stimulating  
4 379 a peripheral nerve, the evoked cortical response is generated by repetitive low frequency  
5 380 stimulation of the target region (CNF/MLR). Outcome measures are response latency (ms) and  
6 381 amplitude ( $\mu\text{V}$ ).

#### 9 382 Motor evoked potentials (MEPs)

10 383 MEPs are tested to evaluate the ability of MLR-DBS enhanced training to induce remodelling  
11 384 of spinal pathways leading to amplification of descending signals. Surface recording electrodes  
12 385 are positioned on the tibialis anterior and the gastrocnemius medialis muscles. Transcranial  
13 386 magnetic stimulation (TMS) is applied on the scalp close to Cz and on the lumbar spine in front  
14 387 of L5. After a test stimulus, the stimulation is increased stepwise up to 100% of the stimulator  
15 388 output and the response is recorded under 5-10% voluntary muscle activation. Total  
16 389 conduction time is measured after scalp stimulation and peripheral conduction time after  
17 390 lumbar stimulation. All measures are recorded before, during and after electrode implantation,  
18 391 and before and after first (week 1 after implantation) and last (6 months after implantation)  
19 392 6MWT assessments. Response latency (ms) and amplitude ( $\mu\text{V}$ ) are compared between  
20 393 timepoints and conditions.

#### 21 394 Local field potentials (LFPs)

22 395 LFPs are measured intraoperatively during probe insertion and postoperatively in case of  
23 396 temporary externalization of the lead. Intraoperative LFPs are measured in the target region,  
24 397 starting 10 mm above the target and ending 5 mm below the target. Postoperative  
25 398 measurements are performed at the 4 contacts of the implanted lead. Signals are band pass  
26 399 filtered (1-500 Hz).

#### 27 400 Electroencephalogram (EEG)

28 401 To reconstruct patterns of specific neuronal activity and their change upon MLR-DBS, non-  
29 402 invasive EEG recordings are performed in the perioperative period and at the last assessment  
30 403 timepoint.

### 31 404 **DBS during behavioural testing and rehabilitative training**

32 405 In the first two weeks after lead implantation, different stimulation parameters (frequency, Hz;  
33 406 pulse width,  $\mu\text{s}$ ; amplitudes, mV) are tested during rest and locomotor training in order to  
34 407 identify optimal stimulator settings including safety limits for each patient individually. The most  
35 408 promising monopolar stimulation settings identified intraoperatively (frequency, pulse width)  
36 409 are applied systematically first via lead contact 2 with varying voltages. In case of failure to  
37 410 induce motor responses or occurrence of side effects at already low voltages parameters will  
38 411 be adapted (frequency, pulse width, polarity, lead contact) sequentially depending on each

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3 412 patient's efficacy and side effect profile. Subsequently, one set of parameters eliciting the best  
4 413 motor responses without side effects is chosen for rehabilitative training (e.g. 20 Hz, 420  $\mu$ s,  
5 414 suprathreshold intensity) and programmed to the patient programming device (up to three  
6 415 additional combinations could be additionally programmed to the device if needed). After two  
7 416 weeks, patients are discharged home or to a rehabilitation clinic located close to home.  
8 417 Training intensity is monitored and ensured by regular follow-ups by phone and by online  
9 418 activity monitoring via wearable sensors mounted to the patient's wrists, ankles and  
10 419 wheelchair. Behavioural testing is performed with and without stimulation during each follow-  
11 420 up visit using the stimulation parameters applied during training.

### 17 421 **Study endpoints**

18 422 The primary endpoint of the DBS-SCI study is improvement of locomotor function, represented  
19 423 by an increased distance covered during the 6MWT when comparing performance at the 6  
20 424 months timepoint with and without DBS with performance at baseline. Additionally, a variety of  
21 425 secondary endpoint assessments are performed (Table 2). Table 3 summarizes timing and  
22 426 schedule of the respective primary and secondary endpoint assessments.

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428 **Table 2 – Primary and secondary endpoint measures.**

Primary endpoint measure	Secondary endpoint measures
6 Minute Walking Test (6MWT) at 6 months follow-up vs. baseline	6 MWT at follow-up timepoints other than 6 months post-implantation
	10 Meter Walking Test (10MWT)
	Timed Up and Go Test (TUG)
	Kinematic assessments (FLOAT)
	Spinal Cord Independence Measure (SCIM III)
	Walking Index for Spinal Cord Injury (WISCI II)
	Activity counts (patient's overall activity level)
	Electrophysiological measurements*
	Quality of life (SF-36)
	Lower urinary tract (LUT) function**
	Sexual function (FSFI/IIEF)
	Spasticity (MAS)
	Neurological classification of SCI (AIS)
	Upper limb function (GRASSP)
	Level of fatigue (FSS)
	Level of sleepiness (ESS)
	Pain (EPAF, SCIPI)

429 FLOAT = Free Levitation for Overground Active Training. MLR = mesencephalic locomotor region.

430 \*Local field potentials (LFPs); somatosensory evoked potentials (SSEPs); motor evoked potentials  
 431 (MEPs); DBS evoked potentials (DBS-EPs); electroencephalogram (EEG). SF-36 = Short Form Health  
 432 Survey to Assess Quality of Life. \*\*bladder diary, QUALIVEEN questionnaire, urodynamic  
 433 measurements, bladder and renal ultrasound. FSFI = Female Sexual Function Index. IIEF =  
 434 International Index of Erectile Function. MAS = Modified Ashworth Scale. AIS = American Spinal Injury  
 435 Association (ASIA) Impairment Scale. GRASSP = Graded Redefined Assessment of Strength,  
 436 Sensation and Prehension. FSS = Fatigue Severity Scale. ESS = Epworth Sleepiness Scale. EPAF =  
 437 EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal  
 438 Cord Injury Pain Instrument.



439 **Table 3 – Flowchart summarising scheduling and timing of primary and secondary**  
 440 **endpoint assessments.**

Site	Study periods	Screening	Baseline	DBS surgery	Post-implantation phase			IPG implantation	Rehabilitation / Follow-up phase						
					4	5	6*		7*	8	9	10	11		
Visit		1	2	3	4	5	6*	7*	8	Dis-charge	Site	9	10	11	
Day (d) / month (mo)		-90 to -30 d	-10 to -1 d	0	1 to 3 d	4 to 7 d	8 to 9 d	6 to 10 d	14 d +/-3 d			mo 1 +/-3 d	mo 3 +/-1 week	mo 6	
<b>Study inclusion and consent</b>															
University Hospital Zurich/ Balgrist University Hospital	Consenting		X												
	Enrolment	X													
	Patient inclusion by PI		X												
	<b>Imaging</b>														
	X-ray thorax		X							X					
	X-ray skull, abdomen									X					
	Stereotactic cranial CT				2 X										
	Diagnostic MRI (3T)		X												
	<b>Perisurgical examinations</b>														
	Surgical examination (incl. wound check)		X		X	X	X	X	X				X	X	X
	Anaesthesiologic examination			X	X			X	X						
	Neuropsychological assessment		X											X	
	Psychiatric assessment		X											X	
	<b>Surgical procedures</b>														
	DBS lead implantation				X										
	Implantation of IPG or explantation of DBS lead					X (externalization may be skipped and IPG implanted at visit 3)									
	Education in handling of patient programming device									X					
	<b>Electrophysiological assessments</b>														
EMG		X		X								X	X	X	
Microelectrode recording				X											
Nerve conduction		X												X	
Non-invasive EEG		X		X	X	X								X	
MEP, SSEP		X		X	X	X								X	
LFP, DBS-EP				X	X	X									
<b>Clinical assessments</b>															
Balgrist University Hospital	AIS	X	X				X		X			X	X	X	
	WISCI II	X	X				X		X			X	X	X	
	SCIM III	X	X				X		X			X	X	X	
	TUG	X	X				X		X			X	X	X	
	Kinematic assessments	X	X				X		X			X	X	X	
	6MWT	X	X				X		X			X	X	X**	
	10MWT	X	X				X		X			X	X	X	
	AE assessment		X		X	X	X	X	X			X	X	X	X
	Questionnaires: QoL, FSFI, IIEF, ESS, FSS, EAPAF, SCIPI		X										X	X	X
	Questionnaire: MAS	X	X					X					X	X	X
	LUT assessments (Bladder diary, QUALIVEEN, urodynamics, bladder/renal ultrasound)		X												X
	GRASSP		X												X

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3 441 \*If impulse generator (IPG) is implanted at visit 3, visit 6 and visit 7 will be skipped. \*\*Primary endpoint.  
4 442 DBS = deep brain stimulation. IPG = impulse generator. CT = computed tomography. MRI = magnetic  
5 443 resonance imaging. 3T = 3 Tesla. EMG = electromyography. EEG = electroencephalography. LFP =  
6 444 local field potentials. MEP = motor evoked potentials. SSEP = somatosensory evoked potentials. DBS-  
7 445 EP = DBS-evoked potentials. QoL = quality of life. FSFI = Female Sexual Function Index. IIEF =  
8 446 International Index of Erectile Function. ESS = Epworth Sleepiness Scale. FSS = Fatigue Severity Scale.  
9 447 AE = adverse event. AIS = American Spinal Injury Association (ASIA) Impairment Scale. WISCI II =  
10 448 Walking Index of Spinal Cord Injury. SCIM III = Spinal Cord Independence Measure. TUG = Timed Up  
11 449 and Go test. 6MWT = 6 Minute Walking Test. 10MWT = 10 Meter Walking Test. EPAF = EMSCI  
12 450 (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord  
13 451 Injury Pain Instrument. MAS = Modified Ashworth Scale. LUT = lower urinary tract function. GRASSP =  
14 452 Graded Redefined Assessment of Strength, Sensation and Prehension.

### 21 453 **Sample size**

22  
23 454 Based on data on the 6MWT [48,82,83] published in the literature and our clinical experience  
24 455 we estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment  
25 456 start compared to performance at baseline to be clinically relevant. A sample size of five  
26 457 patients provides us with a power ( $1-\beta$ ) of 80% ( $\alpha = 0.05$ ). Founded on previous experience in  
27 458 DBS of the MLR,[84,85] we judge that the selected sample size will provide acceptable clinical  
28 459 validity for the study objectives.

### 33 460 **Statistical analysis**

34 461 Considering the observational nature of this clinical trial, statistics will be restricted to  
35 462 descriptive statistics.

### 39 463 **Trial status**

40 464 The study has started recruiting patients in March 2017. To date, one patient has been  
41 465 successfully included on November 26, 2018. Another patient has been included on March 15,  
42 466 2018, but withdrew consent prior to surgery (screening failure).

### 47 467 **Patient and public involvement**

48 468 Patients or the public were not and will not be involved in the design, conduct, reporting, or  
49 469 dissemination plans of this research.

### 53 470 **ETHICS AND DISSEMINATION**

54 471 The study was approved by the local institutional review board (IRB) of the Ethical Committee  
55 472 of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in  
56 473 January and March 2017. Protocol modifications have to be approved by the local IRB and  
57 474 communicated to trial registries. Before inclusion of a patient, the potential participant is

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3 475 informed orally by the investigator, and all potential participants are additionally provided with  
4 476 a clear and comprehensive information sheet. Sufficient time is given to the potential  
5 477 participant to decide whether to participate or not. If potential participants agree to participate  
6 478 in the study, they are asked to sign a consent form at the moment of inclusion in the study.  
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8 479 The data obtained in the course of the study is treated according to the local data protection  
9 480 law and is handled in strictest confidence. During the study, subjects are identified solely by  
10 481 an anonymized patient identifier. The findings of this trial will be submitted to a peer-reviewed  
11 482 journal and abstracts are presented at relevant national and international scientific  
12 483 conferences. The study was registered on ClinicalTrials.gov (NCT03053791) on February 15,  
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## 485 DISCUSSION

486 Encouraging results on behavioural effects of MLR-DBS in preclinical models of neurotrauma  
487 [16,30] have contributed to the initiation of this first in-man study, which is currently being  
488 carried out at the University Hospitals of Zurich. The primary aim of this study is to improve  
489 motor function and enable locomotion in wheelchair-bound, subchronic and chronic SCI  
490 patients with limited, non-functional ambulatory abilities with MLR-DBS, and to investigate the  
491 clinical feasibility and efficacy of MLR-DBS in humans. Ultimately, we aim at maximizing the  
492 long-term restitution of lost motor functions in patients with severe motor incomplete SCI. A  
493 first patient has been included and implanted successfully, followed by intensive locomotor  
494 training with suprathreshold MLR-DBS.

495 The most important lesson learnt from our previous experience in the treatment of this patient  
496 is that MLR-DBS is safe, feasible and well tolerated. No increase in pain, deterioration of  
497 residual motor or sensory functions, cognitive or emotional disturbances, increase in spasticity  
498 and no incontinence was observed. However, sufficient time has to be allocated to the  
499 identification of optimal stimulation parameters for efficient training to ensue as reference  
500 values from human patients are not yet available. Optimal stimulation parameters will have to  
501 be determined for each patient individually, however, based on the existing literature and our  
502 experience gained from one patient wider pulses (>400  $\mu$ s) seem to be more effective for  
503 enhancement of locomotion and more convenient than shorter pulse widths. LFP  
504 measurements and preliminary results from behavioural testing suggest that lower stimulation  
505 frequencies (8-20 Hz) are appropriate, which is in line with preclinical data.[86] Due to the  
506 heterogeneity and complexity of chronic spinal cord injury with individual therapeutic needs,  
507 standardization of rehabilitative training is challenging. While assessments performed during  
508 each patient's stay at the Balgrist University Hospital are standardized, rehabilitative training  
509 performed prior to study inclusion varies individually as we recruit patients internationally and  
510 include patients after completion of a rehabilitation program as we require a stable neurological  
511 baseline condition prior to electrode implantation. After we discharge our patients they train  
512 individually under our regular surveillance and constant activity monitoring to ensure a  
513 minimum training intensity of each patient. However, given that locomotion parameters like  
514 e.g. speed, stepping frequency and body weight support are highly dependent on stimulation  
515 parameters chosen and since parameters for locomotion induction vary depending on e.g.  
516 lesion size, training cannot be completely identical among study participants. This is therefore  
517 a limitation innate to this type of intervention. In addition, the patient's symptoms, especially  
518 the individual severity degree of muscle spasticity, have an influence on the feasible training  
519 intensity and potentially also on the effect of the stimulation. In this study, medications of each  
520 patient are recorded but modified only if required for medical reasons as we first need to

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3 521 investigate the effect of stimulation as a single-therapy before being able to test combination  
4 522 therapies in follow-up studies.

5 523 Given that this proof-of-concept study is the first to investigate effects of DBS of the cuneiform  
6 524 nucleus, the sample size of this study was intentionally chosen to be small. However, our  
7 525 patients undergo a variety of clinically relevant assessments generating important knowledge  
8 526 for follow-up studies of a greater scale. With the 6 Minute Walking Test as primary outcome  
9 527 we have chosen a simple, internationally standardized and comparable test that can be  
10 528 performed anywhere without requiring sophisticated equipment. It measures the maximal  
11 529 distance covered while walking overground independently with a chosen walking aid for 6  
12 530 minutes. This test is highly clinically relevant as one can also record the patient's functionality  
13 531 in everyday life and analyse its changes over time. We expect a significant increase in the  
14 532 distance walked within 6 minutes and a reduction in the need for assistance when walking 6  
15 533 months post-implantation compared to baseline. Based on preclinical studies that have shown  
16 534 a positive effect of MLR-DBS on temporal execution of stepping movements we additionally  
17 535 expect an increase in maximal walking speed (10 Minute Walking Test), improved overall  
18 536 functional mobility (Time Up and Go Test), more efficient step cycle initiation and  
19 537 implementation (kinematic assessments), and increased overall physical activity (activity  
20 538 counts). As reports on improvements of lower urinary tract function in response to locomotor  
21 539 training are increasing,[87,88] we are additionally measuring a variety of indicators for lower  
22 540 urinary tract function, where we expect changes in efficiency of bladder emptying. The variety  
23 541 of clinical scores generate non-parametric data and are obtained to identify and monitor side  
24 542 effects (e.g. pain) rather than to statistically analyse therapeutic effects. All assessments  
25 543 performed in this study comprise standard tests applied internationally in SCI research that  
26 544 enable us to capture the variety of consequences of an injury to the spinal cord, e.g. sensori-  
27 545 motor disturbances, autonomic nervous system dysfunction, and decreased quality of life.

28 546 A particular challenge remains trajectory planning and lead implantation. Many regions of the  
29 547 brainstem, including the MLR subnuclei, are small and poorly described in humans when  
30 548 compared to the rodent PPN and CNF.[23,28,29] Coordinates known from DBS of the PPN  
31 549 with successful reduction of freezing of gait symptoms in patients with Parkinson's disease  
32 550 [24–27] can be adapted based on landmarks in human and rodent stereotactic atlases in order  
33 551 to localize the CNF in relation to the PPN. However, to increase the accuracy of planned  
34 552 trajectories and intraoperative targeting, a more detailed description of the macro- and  
35 553 microanatomy of the human MLR is urgently needed.

36 554 Another important step in trial design and treatment development is patient selection. In both  
37 555 rodents [16,46,89] and humans,[45] the reticulospinal system is crucial for functional recovery  
38 556 after SCI, and at least a small number of reticulospinal fibres needs to be preserved in order  
39 557 to reactivate lumbar CPGs via MLR-DBS. Thus, patients who have suffered an anatomically

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3 558 complete SCI are not envisioned eligible for MLR-DBS. Fortunately, the majority of SCIs are  
4 559 anatomically incomplete,[4] and reticulospinal fibres are likely to be at least partially spared  
5 560 after SCI in humans [44] due to their scattered projection pattern in the spinal cord white  
6 561 matter.[42,43] Based on preclinical data and experience gained from the first study participant  
7 562 we suggest that patients with an incomplete SCI and residual proprioceptive function, who are  
8 563 able to stand, but suffer from deficient stepping initiation and walking function are most likely  
9 564 to benefit from MLR-DBS-enabled and -enhanced training. To allow for an integration of the  
10 565 effects of MLR-DBS into the anatomically still plastic spinal system during early phases after  
11 566 spinal cord injury, we are currently adapting the original study protocol so that patients can be  
12 567 included as early as 3 months after injury provided a stable neurological condition for the  
13 568 detection of stimulation-induced effects. Stratification of patients will be based on the expected  
14 569 outcome of walking function predicted by the 6MWT. Patient recruitment and screening are  
15 570 currently ongoing.

16 571 Our preliminary results from one study patient show that MLR-DBS is feasible and safe. The  
17 572 efficacy of MLR-DBS to enhance training and promote functional recovery in human SCI  
18 573 patients can now be tested in an appropriate number of individuals.

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584 2018 in Edinburgh, Scotland, and the “EANS Trauma & Critical Care Update meeting” 2018 in  
585 Lund, Sweden.

## 586 **Authors' contributions**

587 LHS and ASH contributed equally to the manuscript and are joint first authors. MES, LR, and  
588 ACu are joint senior authors. LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study,  
589 created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR  
590 perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function  
591 and perform testing and analysis. MS, MH, CRB, and LI designed and conduct  
592 electrophysiological measurements. TMK conceptualized and performs assessments of lower  
593 urinary tract function. IK and AP assist with study coordination and conduct questionnaire-  
594 based assessments. All authors are involved in the development and implementation of the  
595 study as well as in data collection and analysis. ASH and LHS designed the figures and drafted  
596 the manuscript. All authors critically revised the manuscript and approved its final version.

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605 Neurology, University Hospital Zurich.

## 606 **Competing interests**

607 The authors declare that they have no competing interests.

## 608 **Patient consent for publication**

609 Written informed consent for publication of clinical details and/or clinical images was obtained  
610 from the patient. A copy of the consent form is available for review by the editor of this journal.

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3 611 **Ethics approval**

4 612 Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case  
5 613 number BASEC 2016-01104) and Swissmedic (10000316). Protocol modifications have to be  
6 614 approved by the local Ethical Committee of the Canton of Zurich and communicated to trial  
7 615 registries.  
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14 617 **FIGURE LEGENDS**

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16 618 **Figure 1 - Schematic illustration of the reticulospinal system.** (A) Higher central nervous  
17 619 system centres of motion control send their signals to the mesencephalic locomotor region  
18 620 (MLR). The MLR is bilaterally linked to its downstream target, the gigantocellular reticular  
19 621 nucleus (NRG), which gives rise to the reticulospinal tract and drives the central pattern  
20 622 generators (CPG) for motoneuron activation and locomotion. (B-C) Horizontal section of the  
21 623 human (B) and cross section of the rat (C) midbrain at the level of the superior colliculi depicting  
22 624 the MLR (B – landmarks based on Afshar et al.[90]; C – landmarks based on Paxinos et al.[91]).  
23 625 CNF = cuneiform nucleus. PPN = pedunculopontine nucleus.  
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3 627 **Figure 2 - Schematic illustration of MLR-DBS.** (A) After incomplete SCI, spared fibres of the  
4 628 reticulospinal tract are not sufficient to properly convey motor signals to sublesional locomotor  
5 629 circuits (CPG). The CPGs are thus deprived of their central input. However, these local rhythm  
6 630 generators remain intact. (B) MLR-DBS can recruit spared fibres of the reticulospinal tract  
7 631 system, enabling them to reactivate sublesional motor circuits. (C) Summary. MLR =  
8 632 mesencephalic locomotor region. NRG = gigantocellular reticular nucleus. SCI = spinal cord  
9 633 injury. CPG = central pattern generators. DBS = deep brain stimulation. (A-B) was modified  
10 634 from Hofer and Schwab, Curr Opin Neurol, 2019 [3], with permission.

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3 636 **Figure 3 – Study timeline.** Patients with a motor incomplete SCI at the level of T10 or above  
4 637 and at least 6 months of recovery after injury are eligible to undergo screening for study  
5 638 participation. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance  
6 639 imaging, and electrophysiological measurements. 1-3 months after study enrolment, baseline  
7 640 testing is performed, followed by unilateral electrode implantation at the less severely affected  
8 641 side 1-10 days later. During surgery, the surgeon decides whether lead and impulse generator  
9 642 (IPG) will be implanted during one session, or whether the lead will be temporarily externalized,  
10 643 depending on intraoperative testing results. In case of lead externalisation, an evaluation  
11 644 period ensues where the patient's responsiveness to MLR-DBS and potential negative side  
12 645 effects are assessed. In case of unsatisfactory results or withdrawal of consent, the lead is  
13 646 removed, and the patient is registered as a study dropout. In case of satisfactory testing, the  
14 647 lead is internalized and the IPG is implanted. After complete implantation, follow-up testing  
15 648 ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged  
16 649 from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will  
17 650 undergo rehabilitative training with DBS at settings predefined during the first 2 weeks after  
18 651 implantation. SCI = spinal cord injury. mo = month(s). d = day(s). wks = weeks. FU = follow-  
19 652 up. TR = training. DBS = deep brain stimulation.

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3 654 **Figure 4 – Target area definition and electrode positioning.** The MLR can be targeted by  
4 655 aiming anterior to the inferior colliculi (IC), lateral of the periaqueductal grey (PAG), and slightly  
5 656 posterior to the central tegmental tract (CTT).[90,92] (A) Coronal, (B) axial, and (C) sagittal  
6 657 view of the mesencephalon of the first patient successfully included in the DBS-SCI trial,  
7 658 showing the localization of the implanted lead (red dot in light grey area). S = superior. I =  
8 659 inferior. L = left. R = right. A = anterior. P = posterior.

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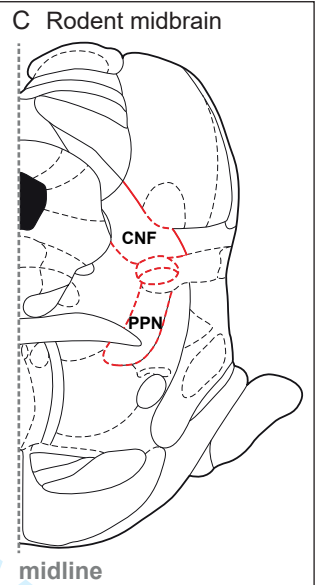
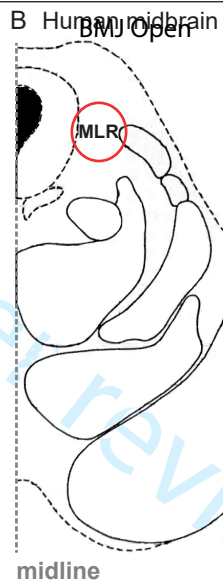
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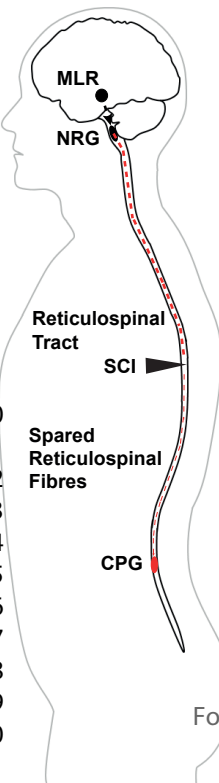
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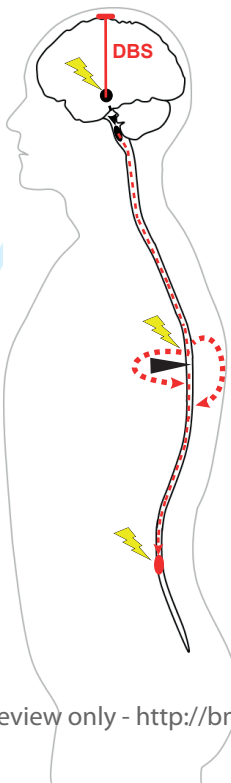
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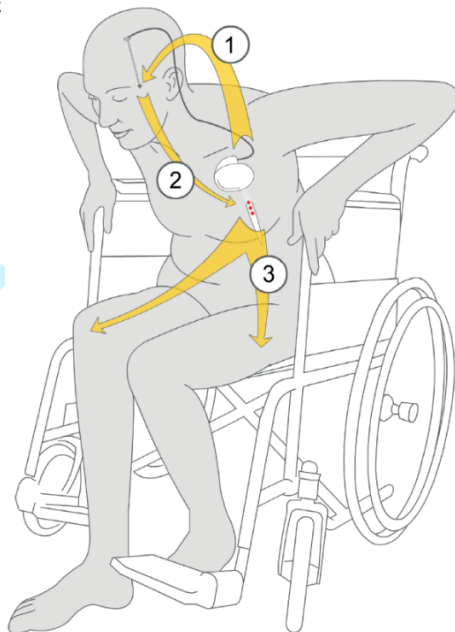
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Unilateral activation of the MLR with DBS

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Spared fibres of the spinal cord bypass the lesion and transfer the signal

3

Activation of CPGs below the injury initiates locomotion



Individual decision by surgeon

Lead externalisation + evaluation\*\*\*

Lead+IPG implant

Hospital discharge

2 wks FU

1 mo FU

3 mo FU

6 mo FU

TR+DBS testing

Rehabilitative TR with DBS

Lead removal (dropout)

Lead internalisation +IPG implant

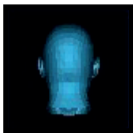
6 Patient enrolment, informed consent

7 Patient inclusion, informed consent

8 \*\*\* Lead will be removed in case of negative side effects or lack of response

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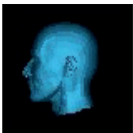
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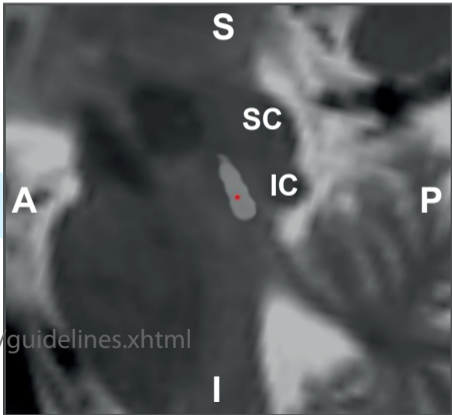
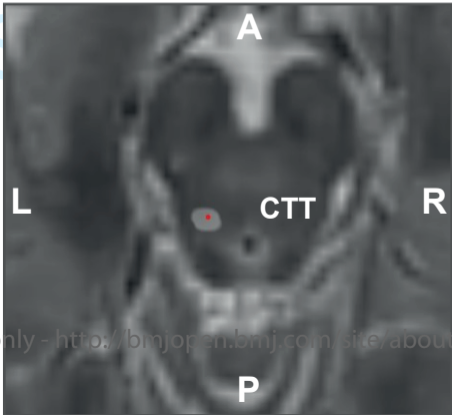
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	<p>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</p> <p><i>A phase I/II open-label multicenter trial to evaluate safety and preliminary efficacy of unilateral deep brain stimulation of the mesencephalic locomotor region in patients with incomplete spinal cord injury (DBS-SCI).</i></p> <p><i>See ClinicalTrials.gov and full study protocol for original study title, manuscript title is found on manuscript page 1.</i></p>
Trial registration	2a	<p>Trial identifier and registry name. If not yet registered, name of intended registry</p> <p><i>Registered on clinicaltrials.gov (NCT03053791, DBS-SCI).</i></p> <p><i>See manuscript pages 1 and 19.</i></p>
	2b	<p>All items from the World Health Organization Trial Registration Data Set</p> <p><i>See ClinicalTrials registry and full study protocol.</i></p>
Protocol version	3	<p>Date and version identifier</p> <p><i>Latest approved (Ethical Committee of the Canton of Zurich) study version: version 5, 12.09.2019.</i></p> <p><i>See ClinicalTrials.gov and full study protocol.</i></p> <p><i>See manuscript page 18 for initial study approval.</i></p>

## Funding

## 4 Sources and types of financial, material, and other support

*Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich. No specific research grant has been declared for this study. The funding sources had no influence on the design of this study and the writing of this manuscript, and will not have any influence on study execution, data analysis, data interpretation, or decision to publish results.*

*See manuscript page 23.*



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Roles and responsibilities

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See manuscript page 1.

*LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis.*

See manuscript page 23.

1  
2 5b Name and contact information for the trial sponsor  
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11 *See [ClinicalTrials.gov](http://ClinicalTrials.gov) and full study protocol.*

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18 5c Role of study sponsor and funders, if any, in study design; collection,  
19 management, analysis, and interpretation of data; writing of the report;  
20 and the decision to submit the report for publication, including whether  
21 they will have ultimate authority over any of these activities  
22

23  
24 *The funding source had no role in the design of this study and will not*  
25 *have any role during its execution, analyses, interpretation of the data,*  
26 *or decision to submit results. The authors have no competing interests*  
27 *to declare.*  
28

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30 *See manuscript page 23.*  
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34 5d Composition, roles, and responsibilities of the coordinating centre,  
35 steering committee, endpoint adjudication committee, data  
36 management team, and other individuals or groups overseeing the  
37 trial, if applicable (see Item 21a for data monitoring committee)  
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## 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

*Briefly: A spinal cord injury (SCI) is a devastating event with an immediate impact on an individual's health and quality of life. Even though most spinal cord injuries are clinically incomplete, major neurological and functional recovery plateaus after three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of CNS targets, e.g. electrical spinal cord stimulation or deep brain stimulation, has aroused scientific interest in recent years with some encouraging results. In deep brain stimulation (DBS) the mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command center that controls the initiation and maintenance of locomotion, is considered a promising target. Animal experiments have shown that MLR-DBS can acutely induce swimming and walking in rats with spinal white matter destructions of >85%. Promising pre-clinical data and the minimally-invasive nature of DBS have led to the initiation of this study to investigate the therapeutic potential of MLR-DBS to improve recovery of gait in a small cohort of patients.*

*See manuscript pages 2 and 4-5.*

6b

Explanation for choice of comparators

*The study comprises no comparators, performance will be compared between different timepoints. The presence of an SCI will be documented by neuroimaging and the risk of paraplegia resulting from other origins can be excluded. Therefore, a mere placebo-effect resulting in improvement of the ability to walk is extremely unlikely. A control group undergoing sham-surgeries is not necessary at this early stage of research on this topic.*

*See manuscript page 6.*

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- Objectives 7 Specific objectives or hypotheses
- We hypothesize that MLR-DBS can modulate spared fibers of the reticulospinal tract system that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking. We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.*
- See manuscript pages 5 and 20.*
- 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, noninferiority, exploratory)
- Briefly: The DBS-SCI trial is a prospective one-armed multi-centre study. The trial is considered successful if the patient's performance in the 6 minutes walking test (6MWT, primary outcome measure) 6 months after treatment start is at least 30% better compared to performance at baseline.*
- See manuscript pages 2 and 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

*Briefly: The trial is conducted and data are collected at two sites in Zurich, Switzerland: the University Hospital Zurich (Departments of Neurosurgery and Neurology, both specialized in deep brain stimulation), and the Spinal Cord Injury Center of the Balgrist University Hospital (specialized in the management of acute and chronic SCI including neurorehabilitation). The study is open to national and international patients, however, basic understanding of German or English is required.*

*See manuscript page 6 and 20.*

1  
2 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility  
3 criteria for study centres and individuals who will perform the  
4 interventions (eg, surgeons, psychotherapists)

5  
6 *Addressed in "Inclusion and exclusion criteria" section of manuscript.*

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8 *Inclusion criteria:*

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- *Informed consent*
  - *Participation in two assessment sessions before enrolment*
  - *Willingness and ability to comply with the protocol and to attend all required study training and visits*
  - *Female or male*
  - *Age 18-75*
  - *Motor incomplete SCI*
  - *Level of lesion at or above T10, based on AIS level, preservation of sacral function*
  - *Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition*
  - *Minimum 6 months of recovery after SCI*
  - *Completed in-patient rehabilitation program*
  - *WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters*
  - *Stable medical and physical condition*
  - *Adequate care-giver support and access to appropriate medical care in patient's home community*

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32 *Exclusion criteria:*

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- *Enrolment of the investigator, her/his family members, employees and other dependent persons*
  - *Limitation of standing and walking function based on accompanying (CNS) disorders*
  - *Cardiovascular disorders*
  - *Implanted technical devices*
  - *Significant autonomic dysreflexia*
  - *Cognitive disorders/brain damage*
  - *Drug refractory epilepsy*
  - *Severe joint contractures disabling or restricting lower limb movements*
  - *Haematological disorders with increased risk of bleeding*
  - *Participation in another study with investigational drug within 30 days preceding and during the present study*
  - *Congenital or acquired lower limb abnormalities*
  - *Women who are pregnant or breast feeding or planning a pregnancy during the course of the study*
  - *Lack of safe contraception*
  - *Inability to follow the procedures of the study*
  - *Known or suspected non-compliance, drug or alcohol abuse*
  - *Current or prior malignancy*

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*See manuscript pages 6-7.*

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2 Interventions 11a Interventions for each group with sufficient detail to allow replication,  
3 including how and when they will be administered  
4  
5 *Interventions and assessments are described in detail in study*  
6 *protocol.*  
7  
8 *Briefly:*  
9  
10 *Intervention model: single group assignment (single group of patients*  
11 *with incomplete SCI), single armed study, all patients receive*  
12 *treatment.*  
13  
14 *Procedure:*  
15  
16 • *Implantation of a deep brain stimulation system (electrodes*  
17 *into the mesencephalic locomotor region and Medtronic Activa*  
18 *SC impulse generator into pectoral or abdominal region).*  
19  
20 • *Deep brain stimulation of mesencephalic locomotor region*  
21 *during rehabilitative training with regular follow-ups until 6*  
22 *months after implantation.*  
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25 See manuscript pages 6, 8-15, Table 2, Table 3, Figure 3.  
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- 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)

*Should a subject's participation in the investigation be discontinued, the reason for discontinuation, e.g. safety concerns, must be documented in the source documents. The Sponsor may terminate the study prematurely according to certain circumstances, for example: ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, or early evidence of benefit or harm of the experimental intervention. Participants may withdraw from participation at any time without need to give reasons. If the patient wishes so, the implanted DBS system will be surgically removed. The procedure will not be charged from the patient or his health insurance. The Investigator may decide to withdraw a subject from the investigation at any time. The investigators must make every effort to contact the subject to ascertain the reason for missed appointments if a subject does not return for follow-up assessments. Correspondence with the subject is necessary for regular withdrawal from pending follow-up.*

*The Study Protocol, Case Report Forms, Informed Consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Any change affecting the subject requires that the subject is informed about the change(s). An updated signed and dated informed consent shall be obtained from the investigator and the study participant, no later than during the subject's next follow-up visit under the scope of this investigation.*

*See original study protocol and manuscript pages 6, 18-19, and 35.*



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- 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

*Initially, all participants are informed in detail about the study, its background and goals, the importance of training intensity, and the importance of adherence to the study plan. At follow-ups, feedback sessions are performed and experience between participants and investigators is exchanged. Regular correspondence with the subjects additionally ensures adherence to intervention protocols. Subjects are asked to document their daily activities and training sessions, which is regularly reported to the investigators in order to monitor training frequency and intensity (in case of home training or training in an external rehab center). In addition, physical activity during training and daily life is monitored by wireless sensors mounted to the patient's wrists, ankles and wheelchair, and data are regularly transferred via SSL-encrypted links (https) established between sites (e.g. a patient's home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).*

*See original study protocol and manuscript pages 6, 14, 20.*

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- 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

*Prior to surgery, all medication that has blood-thinning effect (effect on blood coagulation or platelet function, e.g. Aspirin, Plavix, Marcoumar, Valproic acid, Gingko) is prohibited. The patients are informed by the surgeon prior to surgery about these medications and how they should be discontinued. If there is an indication for continuous intake of an anticoagulant or antiplatelet drug, the patient has to be excluded from the study. Patients with implanted technical devices, e.g. cardiac pacemakers, are not eligible for study participation.*

*See original study protocol and manuscript pages 6-7 and 11.*

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- 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
- Briefly, the primary outcome measure for improvement of ambulation in this study is the gain of covered distance in the 6 minutes walking test (6MWT) at 6 months post implantation compared to baseline level. Additionally, a variety of quantitative and qualitative secondary outcome measures are performed, e.g. kinematic assessments, electrophysiological measurements and questionnaire-based assessments.*
- See manuscript pages 6, 15, Table 2, Table 3, and Figure 3.*
- 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)
- Briefly, patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later (with or without temporary lead externalisation). After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS. See Figure 3 of manuscript.*
- See manuscript pages 6, Table 3, and Figure 3.*

## Sample size

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Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

*Briefly, we aim to include 5 patients in the study who have to complete all preoperative and postoperative examinations until 6 months after surgery, resulting in a total of 11 timepoints. In case of withdrawal of participation or arising complications (dropouts and incomplete follow-up), we aim to include two more patients (replacement of dropouts/withdrawal). The number of subjects is based on the aim of gaining information on treatment effectiveness with adequate safety. Preliminary studies of PPN stimulation in patients with gait disturbance and falls due to Parkinson's disease have been analyzed in a retrospective review by Morita et al., 2014. Sample sizes ranged from 1 to 14 in 12 publications. We estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment start compared to performance at baseline to be clinically relevant. A sample size of five patients provides us with a power (1- $\beta$ ) of 80% ( $\alpha = 0.05$ ). We judge that the selected sample size, based on previous experience in deep brain stimulation of the MLR, will provide acceptable clinical validity for the study objectives.*

*See manuscript pages 6, 18, 21.*

1  
2 Recruitment 15 Strategies for achieving adequate participant enrolment to reach  
3 target sample size  
4  
5 *In summary, all candidate patients, namely patients able to stand with*  
6 *or without walking aid and with a stable neurological condition, are*  
7 *screened and have to meet all of the inclusion and none of the*  
8 *exclusion criteria. Subjects will undergo preoperative examinations*  
9 *(e.g. MRI scans of the head and spine, neuropsychological,*  
10 *psychiatric and sleep status assessments etc.) according to our*  
11 *standard protocols of DBS for movement disorders, based on*  
12 *certification criteria of highly-specialized-medical DBS centers in*  
13 *Switzerland. Neurological assessments for SCI related impairment as*  
14 *defined by the study protocol are performed at the Spinal Cord Injury*  
15 *Center of Balgrist University Hospital. The subject population enrolled*  
16 *in this investigation will be comprised of male and female patients*  
17 *from our out-patient clinic at Balgrist University Hospital or from*  
18 *international volunteers actively contacting the investigators based on*  
19 *information obtained from study registries. Patients who do not meet*  
20 *all in- and exclusion criteria are not eligible to participate in this*  
21 *investigation. There will be no specific gender distribution as gender*  
22 *specific differences concerning efficacy and safety of the*  
23 *investigational diagnostic process are not to be expected.*  
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25 See manuscript pages 6-7.  
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### 39 **Methods: Assignment of interventions (for controlled trials)**

#### 40 Allocation:

- 41  
42 Sequence 16a Method of generating the allocation sequence (eg, computer-  
43 generation generated random numbers), and list of any factors for stratification.  
44 To reduce predictability of a random sequence, details of any planned  
45 restriction (eg, blocking) should be provided in a separate document  
46 that is unavailable to those who enrol participants or assign  
47 interventions  
48  
49 N/A  
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52 Allocation 16b Mechanism of implementing the allocation sequence (eg, central  
53 concealment telephone; sequentially numbered, opaque, sealed envelopes),  
54 describing any steps to conceal the sequence until interventions are  
55 assigned  
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57 N/A  
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2	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
3			and who will assign participants to interventions
4			
5			N/A
6			
7	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
8	(masking)		participants, care providers, outcome assessors, data analysts), and
9			how
10			
11			N/A
12			
13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
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Or peer review only

## Methods: Data collection, management, and analysis

Data collection methods 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

*Addressed in “Study design”, “Clinical assessments”, and “Electrophysiological assessments” sections, and Table 2 and Table 3 of manuscript.*

*The primary outcome measure (6-minute walking test) is an internationally recognized test to assess walking capacity in spinal cord injured patients, widely used in clinical trials and clinical routine. During the 6MWT, the patient is accompanied by an experienced investigator (physiotherapist).*

*Using a variety of standardized, well-known and widely used quantitative, qualitative and questionnaire-based methods as secondary outcome measures, the study additionally collects a big data set on motor, sensory, autonomic function and quality of life. For example, the WISCI (Walking Index for Spinal Cord Injury) is frequently used in clinical trials to assess walking function on an ordinal scale, and it captures the extent and nature of assistance a person with SCI requires to walk. To address the burden of neurogenic lower urinary tract dysfunction on patient’s quality of life after SCI and to analyse the effect of MLR-DBS on recovery of lower urinary tract function, a combination of qualitative (bladder diary, validated questionnaire Qualiveen) and quantitative assessments (urodynamic measurements, renal ultrasound) of bladder function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.*

*See manuscript pages 6, 9-15, Table 2, Table 3.*

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- 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

*Regular correspondence with the subjects in addition to regular follow-ups promotes retention and adherence to intervention protocols. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material. In case of complete implant removal, the patients will receive a short-term follow-up after 4 to 6 weeks by the surgeon to assess wound-healing and outcome of surgery. Afterwards, the clinical follow-up for SCI will be performed at the Balgrist University Hospital according to clinical standards. In case the patient withdraws from the study but refuses removal of the implants, clinical follow-up will be performed as well at the Department of Neurosurgery, University Hospital of Zurich, and at the Balgrist University Hospital according to clinical standards. In case of withdrawal, the patient's study related data will remain in the study. See original study protocol and manuscript page 6, 14-15, 20, and 35.*

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

*Data management system: All data will be entered in a case report form (CRF). Every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors. Overall, the PI is responsible for data handling. The PI and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Investigational data shall be analyzed by the PI and may be transferred to a location outside of Switzerland and/or any other regulatory authority. All data from the CRFs will be transferred to an electronic database by the study coordinator at USZ. All paper CRFs and other documents will be scanned and stored as PDF files. Data transfer will be overseen and double-checked by the PI personally to prevent copy failures.*

*Data security, access and backup: According to corresponding national laws the patient must declare in writing that he or she agrees to the recording of his or her medical data, respectively, and if necessary, the reporting to national health authorities. The CRF and submitted source data are archived by the data owner (PI) for at least 15 years as required by national law. The investigator keeps originals of all source data and an original dated and signed duplicate of the patient consent form of each patient together with other essential study documents at the study center in accordance with the national law. The electronic database and scans of paper CRFs and documents will serve as backup and vice versa.*

*Electronic and central data validation: The investigator confirms with his or her signature on the CRF that all statements and data are complete and correct. All incoming CRF are checked for plausibility and completeness. If necessary, the investigator/study nurse will add missing data or correct inconsistent statements. Any change or correction to data reported on a CRF shall be tracked. Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the CRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall be explained in writing.*

*See original study protocol.*



Statistical  
methods

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

*Statistics will be restricted to descriptive statistics. The trial is  
considered successful if the patient's performance in the 6MWT has  
improved by at least 30% at 6 months after treatment start compared  
to baseline (two-samples t-test).*

*See manuscript page 18.*

20b Methods for any additional analyses (eg, subgroup and adjusted  
analyses)

N/A

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)

N/A

**Methods: Monitoring**

For peer review only

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- Data monitoring 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
- Monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study. All original data including all patient files, progress notes and copies of laboratory and medical test results will be available for monitoring. The monitor will review all or a part of the CRF/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. The investigator's site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure monitoring. A study specific monitoring plan, developed according to the CTC's SOP on monitoring activities, regulates extent, frequency and nature of monitoring activities. A quality assurance audit/inspection of this study may be conducted by the cantonal ethical committee (CEC) and by Swissmedic. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and will answer any questions arising. All involved parties will keep the patient data strictly confidential.*
- See original study protocol.*
- 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. The regulatory authorities receive an annual safety and interim report.*

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- 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
- Every abnormal finding that appears for the first time or worsens during the course of the study will be recorded on the CRF and reported as adverse event. Adverse events (e.g. wound infections) will be interrogated for at each contact between the responsible investigator and the study subject. All pathological and clinically relevant findings in physical and neurological examinations, vital signs, clinical chemistry, hematology, and during surgery will be documented as adverse events. Complications related to assessments (e.g. falls during walking tests) will be reported as adverse events.*
- See original study protocol.*
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- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
- A quality assurance audit of this study may be conducted by the cantonal ethical committee and by Swissmedic. The quality assurance auditor will be independent from the investigators and sponsor, and have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will grant the auditor access to the source data/documents and will answer any questions arising during the audit. All involved parties will keep patient data strictly confidential.*
- See original study protocol.*

## Ethics and dissemination

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5 Research ethics 24 Plans for seeking research ethics committee/institutional review board  
6 approval (REC/IRB) approval  
7  
8 *Ethical approval has already been obtained from the Ethical*  
9 *Committee of the Canton of Zurich (case number BASEC 2016-*  
10 *01104) and Swissmedic (10000316) in 2017. Latest approved protocol*  
11 *version: version 5, 12.09.2019.*  
12  
13 *See manuscript pages 2, 18-29, 24.*

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16  
17 Protocol 25 Plans for communicating important protocol modifications (eg,  
18 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties  
19 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
20 regulators)  
21  
22 *Amendments are sent to and evaluated by the Cantonal Ethical*  
23 *Committee and Swissmedic. Substantial amendments are only*  
24 *implemented after approval by the Cantonal Ethical Committee and*  
25 *Swissmedic, respectively. Any change affecting the study participants*  
26 *requires that the subject is informed about the change(s). An updated*  
27 *signed and dated informed consent will be obtained from the subject*  
28 *by the investigator, no later than during the subject's next follow-up*  
29 *visit under the scope of this investigation.*  
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31 *As addressed in the "Discussion" section of the manuscript, an*  
32 *amendment to the study protocol is currently being written in order to*  
33 *include patients already 3 months after injury (instead of 6).*  
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35 *See manuscript pages 18-19, and 22.*  
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2 Consent or assent 26a Who will obtain informed consent or assent from potential trial  
3 participants or authorised surrogates, and how (see Item 32)  
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5 *Before inclusion of a patient, the potential participant is informed by*  
6 *the investigator about the nature and purpose of the trial, the*  
7 *procedures involved, expected duration, potential risks and benefits,*  
8 *and any discomfort that might occur. Each participant will be informed*  
9 *that the participation is voluntary and that he/she may withdraw*  
10 *consent from the study at any time. Withdrawal of consent will not*  
11 *affect the patient's subsequent medical assistance and treatment. The*  
12 *participant is informed that his/her medical records may be examined*  
13 *by authorized individuals other than their treating physician. All*  
14 *participants are provided with a participant information sheet and a*  
15 *consent form describing the study and providing sufficient information*  
16 *for patients to make an informed decision about their participation in*  
17 *the study. Sufficient time will be given to the participant to decide*  
18 *whether to participate or not. Depending on the date of screening, the*  
19 *time frame is 20-80 days before hospitalization.*  
20  
21 *The patient information sheet and the consent form have been*  
22 *reviewed and approved by the Cantonal Ethical Committee and*  
23 *Swissmedic. The formal consent of a participant is obtained before the*  
24 *participant undergoes any study procedure. The participant has to*  
25 *read and consider the statement before signing and dating the*  
26 *informed consent form, and is given a copy of the signed document.*  
27 *The consent form is also signed and dated by the investigator (or his*  
28 *designee), and will be retained as part of the study records.*  
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30 *See original study protocol and manuscript pages 18-19.*  
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44 26b Additional consent provisions for collection and use of participant data  
45 and biological specimens in ancillary studies, if applicable  
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47 N/A  
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- 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
- All data will be entered in a database as recorded in the CRF and every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's personal information. This separately stored list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.*
- See original study protocol.*
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site
- The authors have no conflicts of interest to declare. Investigators and collaborators receive no financial or other compensation for work rendered in accordance with the study, despite their regular income from their respective affiliations.*
- See manuscript page 23.*
- Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
- After termination of the study, study data will be available for analysis only for persons or institutes assigned by the PI, according to local regulations. Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.*
- The PI maintains all essential clinical investigation documents from prior, during and after the clinical investigation on file at the site. Originals of all study-related report forms, administrative documents, medical records, and a list allowing patient identification will be stored in the study headquarters University Hospital Zurich and Balgrist University Hospital for at least 15 years after completion of the trial.*
- See original study protocol.*

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

*Any damage developed in relation to study participation is covered by the study's insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the PI (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly in the event of health problems or other injuries sustained during or after the course of study. The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential. The patient and his health insurance will not be charged for screening, treatment and follow-up (until 6 months after surgery), but there will be no compensation for participation in the study. Clinical examinations and treatments after completion of the 6 months' follow-up will be charged from the patient's health insurance.*

*See original study protocol.*

Dissemination  
policy

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

*The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international conferences. Results will be communicated to participants in layman's terms.*

*See manuscript pages 2 and 19.*

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- 31b Authorship eligibility guidelines and any intended use of professional writers
- Publication(s) and/or presentation(s) of the study results is encouraged. Neither the sponsor nor the investigators have the right to prevent publication, except for patent or copyright reasons. Staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors, if applicable. A copy of all publications will be sent to the coauthors. The PI will decide about authorship and the sequence of co-authors, including the last author, based on the amount and importance of the contribution to the study as judged by the PI. No professional writers will be used.*
- See original study protocol.*
- 31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
- N/A

### Appendices

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- Informed consent materials 32 Model consent form and other related documentation given to participants and authorised surrogates
- Please see Appendix 1.*
- 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

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.



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Appendix 1 - Model consent form

For peer review only



**Informed consent for participation in a clinical study**

- Please read this document carefully
- Please ask in case of questions or further interest.

<b>Study identifier:</b> (of the local ethics committee)	BASEC 2016_01104
<b>Study title:</b>	Deep Brain Stimulation in patients with incomplete spinal cord injury for improvement of gait Tiefe Hirnstimulation zur Verbesserung des Gehens bei Patienten mit Rückenmarksverletzungen
<b>Responsible institution (Sponsor)</b> (complete address):	Neurochirurgische Klinik, UniversitätsSpital Zürich, Frauenklinikstrasse 10, CH-8091 Zürich
<b>Study site:</b>	UniversitätsSpital Zürich and Uniklinik Balgrist Zürich
<b>Principal investigator:</b> Name, First name:	Lennart Stieglitz MD, Chief of service, Specialist for Neuromodulation Armin Curt MD, Chairman Center for Paraplegia
<b>Participant:</b> Name and first name, date of birth	<input type="checkbox"/> female <input type="checkbox"/> male

- I was informed in detail orally as well as in written form about the purpose, the conduction, about expected effects, possible side-effects, risks and benefits of the study by the signing surgeon.
- My questions concerning my participation in the study were answered satisfyingly. I received the study information of 07.06.2019 Version 2 (two parts) and receive a copy of this informed consent form. I accept the content of the above mentioned study information.
- I participate in this study voluntarily. I can withdraw from participation at any time and will not suffer disadvantages concerning my ongoing medical treatment hence.
- I was informed about other possible treatment options.
- I was given enough time to decide about my participation.
- I was informed, that an insurance company will cover damages resulting from participation in the study, in case I can prove the connection clearly.
- I agree that my general practitioner is informed about my participation in the study: Yes  No .
- In case of incidental findings I want to a)  be informed unconditionally; b)  not informed or c)  I want to leave the decision with the following person: .....
- I know, that my personal data may only be used in coded form for scientific purposes. I agree, that the responsible specialists of the initiator of the study and the local authorities (cantonal ethics committee) may be granted insight into the original data for control purposes, but only under strict compliance with confidentiality.
- I am aware, that the obligations mentioned in the study information are to be obliged during the study. The principal investigator may exclude me from the study at any time with my best interests in mind.

Place, date	Signature study participant
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**Confirmation of the investigator: Hereby I confirm that I informed the participant in detail about the character, importance and relevance of the study.** I will fulfill all legal obligations in connection with this study. Should I learn of aspects that could affect the willingness of the participant to participate during the course of the study, I will inform him/her immediately.

Ort, Datum	Signature of the investigator
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