FULL/LONG TITLE OF THE TRIAL:

A PROSPECTIVE, MULTI-CENTER, RANDOMIZED, PARALLEL-GROUP CONTROLLED TRIAL TO COMPARE CONSERVATIVE VERSUS SURGICAL TREATMENT OF FOOT DROP IN PERONEAL NERVE ENTRAPMENT.

SHORT STUDY TITLE / ACRONYM:

FOOT DROP (**F**ollow-up and **O**utcome of **O**perative **T**reatment with **D**ecompressive **R**elease **O**f The **P**eroneal nerve)

PROTOCOL VERSION NUMBER AND DATE:

Version 3.0; Date 10/03/2023

RESEARCH REFERENCE NUMBERS

Clinical trials.gov Number:	NCT04695834
SPONSOR Number:	UZ Leuven – S62895
KCE Trials Number:	KCE19-1232

■ TABLE OF CONTENTS

■ SIGNATURE PAGE 4
■ STUDY PROTOCOL 14
1 BACKGROUND 14
2 RATIONALE 18
3 ASSESSMENT AND MANAGEMENT OF RISK 20
4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES 21
4.1 PRIMARY OBJECTIVE 21
4.2 SECONDARY OBJECTIVES 21
4.3 ENDPOINTS 21
4.3.1 Primary endpoint 21
4.3.2 Secondary endpoints 22
5 TRIAL DESIGN 23
5.1 FULL-SCALE STUDY DESIGN 23
5.2 FEASIBILITY PILOT STUDY DESIGN 24
6 STUDY SETTING 25
7 ELIGIBILITY CRITERIA 26
7.1 INCLUSION CRITERIA 26
7.2 EXCLUSION CRITERIA 26
8 TRIAL PROCEDURES 27
8.1 RECRUITMENT 27
8.1.1 Patient identification 27
8.1.2 Screening 28
8.2 CONSENT 28
8.3 TRIAL RANDOMISATION 30
8.4 BLINDING 30
8.5 UNBLINDING OF OUTCOME ASSESSOR 31
8.6 BASELINE DATA 31
8.7 TRIAL ASSESSMENTS 33
8.7.1 Time to recovery 34
8.7.2 Electrodiagnostics (EDX) 34
8.7.3 Muscle Power Assessment (Medical Research Council's scale) 35
8.7.4 Isometric dynamometry 36
8.7.5 Six-minute walk test (6MWT) 37
8.7.6 Ability to walk barefoot 39
8.7.7 Stanmore Questionnaire 39
8.7.8 Need for ankle-foot orthosis 40
8.7.9 Gait speed in the 10-meter walk test 40
8.7.10 Sensory Changes 41
8.7.11 Functional Ambulation Categories 41
8.7.12 Quality of life questionnaires 42
8.7.13 Surgical Complications 43
8.7.14 Treatment record 43
8.7.15 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) 44
8.7.16 Return to work at six weeks after randomization 44
8.8 TABLE OF TRIAL PROCEDURES 44
8.9 WITHDRAWAL CRITERIA 46

8.9.1 Loss to follow-up 47
8.10 END OF TRIAL 47
9 TRIAL INTERVENTION 48
9.1 SURGICAL DECOMPRESSION OF THE PERONEAL NERVE AT THE FIBULAR HEAD (NEUROLYSIS) 48
9.2 CONSERVATIVE TREATMENT 49
10 SAFETY RECORDING AND REPORTING 50
10.1 DEFINITIONS 50
10.2 RECORDING OF SAFETY FINDINGS IN FUNCTION OF THE AVAILABLE EVIDENCE 50
10.3 DATA SAFETY MONITORING BOARD 51
10.4 NOTIFICATION OF DEATHS 52
11 STATISTICS AND DATA ANALYSIS 53
11.1 SAMPLE SIZE CALCULATION 53
11.2 SAMPLE SIZE REASSESSMENT 53
11.3 PLANNED RECRUITMENT RATE 53
11.4 STATISTICAL ANALYSIS PLAN 55
11.4.1 Analysis sets 55
11.4.2 Summary of baseline data and flow of patients 55
11.4.3 Primary outcome analysis 56
11.4.4 Secondary outcome analysis 56
11.4.5 Procedure(s) to account for missing or spurious data 57
11.4.6 Other statistical considerations. 57
11.5 DATA COLLECTION FOR ECONOMIC EVALUATION 57
12 DATA HANDLING 59
12.1 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION 59
12.2 DATA HANDLING AND RECORD KEEPING 60
12.3 ACCESS TO DATA 60
12.4 ARCHIVING 60
13 MONITORING, AUDIT & INSPECTION 62
14 ETHICAL AND REGULATORY CONSIDERATIONS 63
14.1 ETHICS COMMITTEE (EC) REVIEW & REPORTS 63
14.2 PUBLIC AND PATIENT INVOLVEMENT 63
14.3 REGULATORY COMPLIANCE 67
14.4 PROTOCOL COMPLIANCE 67
14.5 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL 68
14.6 DATA PROTECTION AND PATIENT CONFIDENTIALITY 68
14.7 FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT 68
14.8 INDEMNITY 68
14.9 ACCESS TO THE STUDY DATA BY KCE AND SIMILAR INSTITUTES IN THE EU 69
14.10 ACCESS TO THE FINAL TRIAL DATASET BY OTHER PARTIES 70
15 DISSEMINATION POLICY 70
15.1 DISSEMINATION POLICY 70
15.2 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS 70
15.3 COMMUNICATION PLAN 71
16 REFERENCES 72

■ SIGNATURE PAGE

The undersigned confirms that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " Directive 2001/20/EC",), and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor, Chief Investigator:		
Signature:		Date: ...../...../.....
Name (please print):		
Position:		
Statistician:		
Signature:		Date: ...../...../.....
Name: (please print):		
Position:		
For acknowledgement on behalf of the funder (KCE):		
Signature:		Date: ...../...../.....
Name (please print):		
Position:		
Principal Investigator Participating Site:		
Signature:		Date: ...../...../.....
Name (please print):		
Position:		

KEY TRIAL CONTACTS

Chief Investigator	Tom Theys – UZ Leuven Department of Neurosurgery Herestraat 49, 3000 Leuven tom.theys@uzleuven.be +32 16 34 42 90
Trial Coordinator	Christophe Oosterbos – Departement of Neurosurgery Herestraat 49, 3000 Leuven christophe.oosterbos@uzleuven.be +32 16 34 52 60
Blinded Researcher	A blinded researcher will be appointed in every participating center. Preferably, the outcome assessor will be an independent physician. This will be finalized in the delegation logs.
Sponsor	Universitaire Ziekenhuizen Leuven Herestraat 49, 3000 Leuven CTC@uzleuven.be +32 16 34 19 98 Although KCE provides funding for the trial, KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and sponsor or co-sponsor shall make no representations whatsoever in this respect.
Funder(s)	Belgian Health Care Knowledge Centre (KCE) Administrative Centre Botanique, Doorbuilding, Boulevard du Jardin Botanique 55, B-1000 Brussels, Belgium Trials@kce.fgov.be 00 32 2 287 33 88
Clinical Trials Unit	Ellen Nijs Ine Vanopdenbosch Clinical Trial Center UZ Leuven Herestraat 49, 3000 Leuven ctc@uzleuven.be +32 16 34 19 98
Statistician	Kris Bogaerts - L-BioStat Kapucijnenvoer 35 bus 7001, 3000 Leuven Kris.Bogaerts@kuleuven.be +32 16 37 33 43

Data Manager	Jill Claes - Clinical Trial Center UZ Leuven Herestraat 49, 3000 Leuven ctc.datamanagement@uzleuven.be +32 16 34 43 91
Committees	Trial Steering Committee Trial Management Group

TRIAL SUMMARY

Trial Title	A PROSPECTIVE, MULTI-CENTER, RANDOMIZED, PARALLEL-GROUP CONTROLLED TRIAL TO COMPARE CONSERVATIVE VERSUS SURGICAL TREATMENT IN PERONEAL NERVE ENTRAPMENT
Short title	FOOT DROP: **F**ollow-up and **O**utcome of **O**perative **T**reatment with **D**ecompressive **R**elease **O**f the **P**eroneal nerve
Trial Design	This is a prospective, multi-center, randomized, parallel-design study. This is a superiority trial: the goal is to prove superiority of surgery to maximal conservative treatment. Subjects will be randomized 1:1 to surgery or to conservative treatment. No cross-over is allowed until the primary endpoint is assessed at 9 months after randomization. After the primary endpoint is assessed, cross-over to surgery is allowed, with extended follow-up at 18 months after randomization (equals 9 months after primary endpoint).
Trial Participants and setting	Patients with electrodiagnostic (EDX)-documented peroneal nerve entrapment with persisting foot drop 10 +/- 4 weeks after onset of symptoms will be included in the trial. Imaging to exclude a compressive mass at the level of the fibular head is required, since these patients are excluded from the trial. Included patients will be allocated to either surgical decompression of the peroneal nerve or maximal conservative treatment.
Intervention	Decompressive release of the peroneal nerve at the level of the fibular head.
Control	Maximal (prolonged) conservative treatment with physiotherapy aiming at muscle strengthening and gait rehabilitation. Allowed: use of foot-ankle orthosis / electrostimulation and other therapies reflecting daily practice.
Primary Endpoint	Difference in distance (in meters) covered during the six-minute walk test between baseline and 9 months after randomization
Secondary Endpoint(s)	Key secondary endpoint: - Time to recovery (defined as the time necessary to cover the minimal age- and sex-specific normal 6MWD AND the time necessary for foot drop recovery to an MRC-score ≥ 4 for ankle dorsiflexion Secondary endpoints: - Ankle dorsiflexion strength at 10 days (surgical group), 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. - Gait assessment at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. - Complications and neurological deficits at 10 days (surgical group), 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization.

	- Health-economic assessment at 6 weeks and 6 months after randomization. - Electrodiagnostics (EDX) at 3 months and 9 months after randomization. - Patient-reported outcome measures at 10 days (surgical group), 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization.
Planned Sample Size	Overall, the study will enrol 182 subjects in 2 treatment arms, 91 subjects per arm. The statistical analysis plan will contain a blinded sample size reassessment to verify if the planned sample size is sufficient to show the minimal clinical important difference. In phase 1, the study will be conducted in 19 centers in Belgium and 1 center in the Netherlands. If the predefined, minimal yearly number of randomizations is not reached, additional centers can be initiated in phase 2.
Treatment duration	The duration of treatment in the conservative arm of the trial is 9 months. Surgery can be performed in day-care setting or through short hospitalisation (up to 2 nights). Postoperative physiotherapy can be variable. If cross-over occurs after 9 months, postoperative treatment is standard of care and depending on the treating physician.
Follow up duration	Primary endpoint is assessed at 9 months. Extended follow-up at 18 months.
Duration of the trial (FPI-CSR)	All patients will be included within 4 years after the last site initiation visit in the phase 1 study centers. Maximal trial duration is 5.5 years.

ROLE OF STUDY SPONSOR AND FUNDER

UZ Leuven as mentioned in KEY TRIAL CONTACT shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. UZ Leuven shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with

the Study Subjects or the Regulatory Authorities as sponsor of the Study. UZ Leuven acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and UZ Leuven shall make no representations whatsoever in this respect.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC monitors trial progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet on average 3 times per year the first year and twice a year thereafter. The TSC is composed of the Chief Investigator (CI), the trial statistician, the trial Project Manager (PM), an independent expert, a representative of other participating centres or groups, up to 2 patients or members of the public, 1 representative of the sponsor, and 1 representative of the funder.

Members of the TSC:

1. Tom Theys, M.D., PhD. Department of neurosurgery, UZ Leuven (Chief Investigator)
2. Robin Lemmens, M.D., PhD. Department of neurology, UZ Leuven
3. Johannes van Loon, M.D., PhD. Chairman of the department of neurosurgery, UZ Leuven
4. Frank Weyns, M.D. Chairman of the department of neurosurgery, ZOL Genk (Representative participating center)
5. Annie Dubuisson, M.D., PhD. Department of neurosurgery, CHU de Liège (Co-chief Investigator)
6. Justus Groen, M.D. Department of neurosurgery, Leids Universitair Medisch Centrum (Representative participating center)
7. Kris Bogaerts, PhD. L-Biostat (Trial statistician)
8. Ine Vanopenbosch, Clinical Trial Center UZ Leuven
9. Nelle Stocquart (Representative KCE)
10. Magdalena Zabrzeska-Schmitt, physiotherapist, UZ Leuven
11. Philip Van Damme, M.D., PhD. Department of neurology, UZ Leuven (Independent expert)
12. Lukas Rasulic, M.D., PhD. Department of neurosurgery, Clinical center of Serbia (Independent expert)
13. Jan Goffin, M.D., PhD. Emeritus professor, former head of the department of neurosurgery, UZ Leuven (Independent expert)
14. Irena Vicchio: Patient representative: ongoing process

There is no need for a true data safety monitoring board (see section 10.3). However, the independent experts (experts that are not directly involved in the trial) will act as an ‘extern advisory board’ to follow up on possible harm (e.g. related to late cross-over to surgery) and to follow up on blinding and accidental unblinding.

Trial Management Group (TMG)

The day-to-day management of the study will be performed by the Trial Management Group (TMG), which is distinct from the TSC.

Members of the TMG:

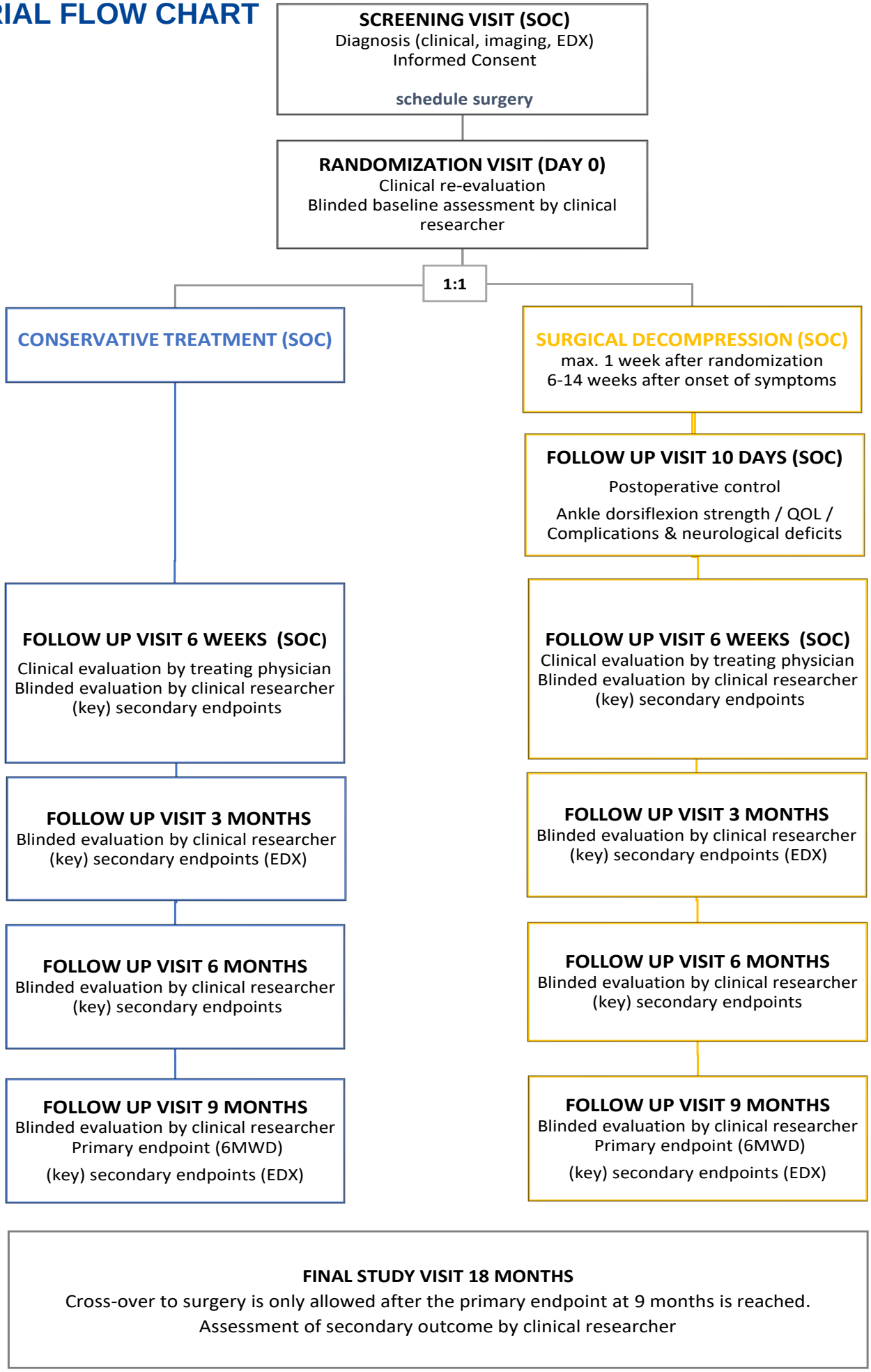
1. Tom Theys, M.D., PhD. Department of neurosurgery, UZ Leuven (chief investigator)
2. Christophe Oosterbos, M.D. Department of neurosurgery, UZ Leuven (project manager)
3. Jill Claes, Clinical Trial Center, UZ Leuven (data manager)
4. Annie Dubuisson, M.D., PhD. Department of neurosurgery, CHU de Liège (co-chief investigator)
5. Kris Bogaerts, PhD. L-BioStat (trial statistician)
6. Sophie Hoornaert, Clinical Trial Assistant, UZ Leuven

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
CA	Competent Authority
CI	Chief Investigator
CMAP	Compound Motor Action Potential
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
EDB	Extensor Digitorum Brevis Muscle
EDX	Electrodiagnostics
EMG	Electromyography
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
KCE	Belgian Healthcare Knowledge Centre
MCID	Minimal clinically important difference
MRC	Medical Research Council

MS	Member State
MS	Multiple Sclerosis
NCS	Nerve Conduction Studies
PI	Principal Investigator
PIS	Participant Information Sheet
PM	Project Manager
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SNAP	Sensory Nerve Action Potential
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health
6MWT	Six-minute walk test
6MWD	Distance covered during the six-minute walk test in meters (six-minute walk distance)

TRIAL FLOW CHART



■ STUDY PROTOCOL

1 BACKGROUND

Peroneal neuropathy is the most common neuropathy in the lower limbs(1-4) and represents the third most common focal neuropathy, after median and ulnar nerve pathology (5, 6). Epidemiologic data on peroneal neuropathy are scarce. Studies from Egypt (7, 8) found a prevalence of symptomatic peroneal neuropathy of 40 per 100.000 inhabitants in a population-based survey, and 19 per 100000 in a community-based study of 42633 subjects. Based on the data from the Egyptian studies (7, 8), 0.6% to 1.2% of all neuropathies are peroneal neuropathies. The reported percentage of 0.6% in the Kandil series is probably an underestimation of the total number of peroneal neuropathies, since all idiopathic neuropathies were reported as a separated category. Cruz-Martinez et al. (9) however, found 150 peroneal neuropathies in a patient database of 1000 neuropathies (15%), contrasting the percentages of Khedr and Kandil. According to Katirji et al.(10), 10% of peroneal neuropathies are bilateral. Motor deficits are frequent and even patients with subclinical peroneal mononeuropathy are at increased risk of falling (11-13). There is no data on the number of subjects with peroneal nerve entrapment suffering from foot drop.

The etiology of peroneal neuropathy is very broad. The nerve can be compressed by cysts and tumors (14), or due to muscle herniation (15). The peroneal nerve is also sensitive to external compression which can result from bracing, wearing a tight cast, habitual crossing of the legs, squatting and kneeling. Peroneal neuropathy is frequently associated with excessive weight loss, as seen after bariatric surgery (3, 16-19) or anorexia nervosa (20); some authors believe that the loss of subcutaneous fat tissue in the area of the fibular head causes increased susceptibility to compression (6, 21). Long-term bedridden patients are also prone to peroneal neuropathy (1, 22, 23). Iatrogenic damage can occur after surgery of the hip, knee and ankle, or even after thoracic-abdominal surgery due to patient positioning. Other potential causes are trauma (23-25) and metabolic disorders (e.g. diabetes mellitus, hypothyroidism) (26).

Given the broad range of causes of peroneal neuropathy, treatment strategies are likely to vary for different subtypes of peroneal nerve pathology. Peroneal neuropathies can be classified as idiopathic, idiopathic with established risk factors (e.g. leg crossing, squatting, weight loss, kneeling, metabolic disorders, bracing, …) and non-idiopathic peroneal neuropathies (e.g. trauma, iatrogenic, cysts and tumors, …). In this proposal, non-idiopathic peroneal neuropathies are not discussed, since these 'subtypes' will be excluded from the trial. The pathology of interest will be referred to as peroneal nerve entrapment. Peroneal nerve pathology in general will be referred to as peroneal neuropathy.

The peroneal nerve is especially vulnerable to compression at the level of the fibular head, due to its superficial course. Here, the nerve dives in the fibular tunnel, defined by the fibular neck, peroneus longus muscle and soleus muscle(27). Figure 1 illustrates the anatomy at the level of the fibular head.

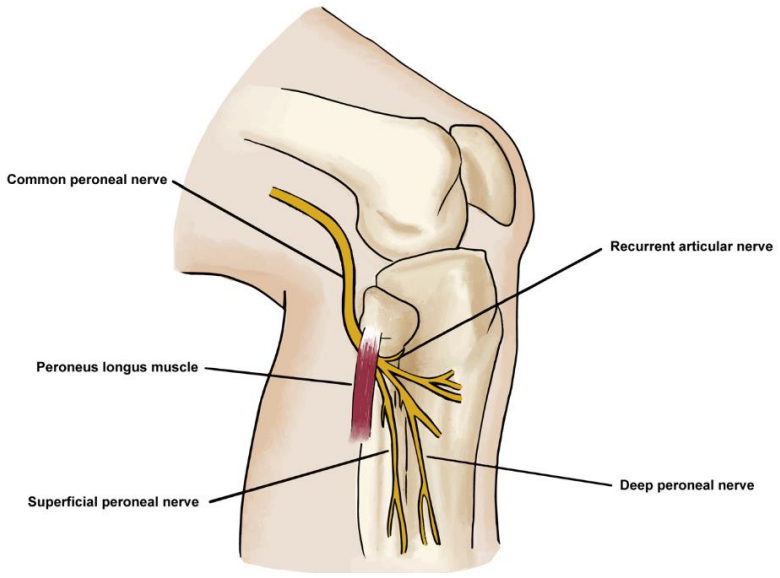


Figure 1 Anatomy of the peroneal nerve at the level of the fibular nerve *(Illustration by Irene Caprara)*.

Conservative treatment of peroneal nerve entrapment consists of physiotherapy using stretching of the calf muscles to prevent contractures, muscle strengthening and gait rehabilitation (28). Physiotherapy exercises are sometimes combined with functional electrical stimulation and electrostimulation has been applied for denervated muscles after peripheral nerve lesions (29-31). Ankle foot orthoses can improve gait parameters and functional ambulation in patients with foot drop (28, 32-34). The available literature on the conservative treatment mainly consists of retrospective series (22, 24, 35-39) describing a very heterogeneous patient population including traumatic and iatrogenic peroneal nerve lesions. The number of patients with peroneal nerve entrapment was low varying between 14 and 33 with a follow-up ranging between three months and three years. Outcome of these retrospective series is summarized in table 1.

One multicenter prospective study of 46 patients (28) documented follow-up data in conservatively treated patients including 13 patients who did not receive any treatment at all due to mild symptoms. After a mean follow-up of 6 months, 39% of the conservatively treated patients (n = 33) needed a foot orthosis to be able to walk and 53% had a normal gait pattern. In patients in whom no conservative treatment was initiated 25% needed a foot orthosis and 63% had a normal gait pattern. Overall, 79% of patients with peroneal nerve entrapment reported improvement of ankle dorsiflexion at 6 months (n = 34). Taking all available literature into consideration, good outcome after conservative treatment for peroneal nerve entrapment varies between 53% and 100% in the literature. When interpreting these range of outcome percentages, one should realize that outcome measures differ between the studies. If data was available, good outcome was translated to an MRC-score ≥ 4 for ankle dorsiflexion. If data was not available, outcome measure of the study was documented.

Sangwan et al. (40) reported the results of conservative treatment of foot drop due to prolonged squatting in a prospective case series of 30 patients (34 limbs). Thirty-two foot drops fully recovered after 3 to 9 weeks. The other 2 patients recovered fully after 16 and 20 weeks (100%). Cruz-Martinez (9) prospectively documented the clinical evolution of foot drop in 30 patients receiving no or conservative treatment. Twenty-six patients fully recovered after a period of 3 weeks to 3 months, three other patients reported minimal weakness (97%). The severe muscle weakness in 1 patient did not improve after 6 months (but recovered within 2 weeks after neurolysis). Although these findings are not confirmed in other case studies, these series describe possible recovery of foot drop in an early stage with conservative therapy. These findings are important regarding the timing of randomization (see 5.1 full-scale study design).

Fares et al. (41) reviewed foot drop after bariatric surgery in 21 cases. Seven patients were treated conservatively and improved (100%). Two other foot drops resolved spontaneously. Since the degree of recovery was often not specified, this study was not included in Table 1.

Author	**Type of study**	**Number of patients**	**Outcome measure**	**Good outcome (%)**	**Follow-up**
Aprile (24)	Retrospective	14	Improvement ankle dorsiflexion or absence of gait difficulties	71%	3 months – 3 years
Berry (37)	Retrospective	14	MRC-score ankle dorsiflexion ≥ 4	64%	up to 1 year
Bsteh (38)	Retrospective	25	MRC-score ankle dorsiflexion ≥ 4	88%	9.3 months (mean)
Sipahioglu (39)	Retrospective	14 (16 limbs)	MRC-score ankle dorsiflexion ≥ 4	87.5%	Until full recovery (max. 13 weeks)
Aprile (28)	**Prospective**	33* 34	Absence of gait difficulties	53% 79%	6 months

			Improvement of ankle dorsiflexion		
Sangwan (40)	**Prospective**	30 (34 limbs)	MRC-score ankle dorsiflexion ≥ 4	100%	Mean: 28.2 months
Cruz-Martinez (9)	**Prospective**	30	MRC-score ankle dorsiflexion ≥ 4	97%	Until recovery (max. 7 months)

Table 1 Outcome after conservative treatment. Good outcome is defined as an MRC grade ≥ 4 for ankle dorsiflexion. * Patients with mixed etiology of peroneal neuropathy.

The surgical approach for entrapment at the fibular head aims at decompressing the peroneal nerve as it dives under the peroneus longus muscle. Similar to the literature on conservative treatment most studies on the surgical management concerned retrospective patient series (3, 31, 42-54). Some studies had a very heterogeneous patient population hampering extraction of required data, or did not discuss patients with peroneal nerve entrapment (31, 46, 48, 52-54). Most series suffered from a low sample size (the smallest study included only 12 patients) with a great variability in timing between symptom onset and surgery ranging from weeks to years. On average patients were operated after 4.6 months (range:1 month -27 months for the included case series) with a follow-up duration ranging from 11 months to 7 years.

We identified 2 prospective studies, one describing 14 patients with a follow-up of one year after surgery (55) recording improvement of ankle dorsiflexion in 13 of 14 patients (93%), with half of the patients having normal ankle dorsiflexion at one year. The prospective series of Nirenberg (56) described the outcome of 17 patients with peroneal neuropathy (of unknown etiology) and a follow-up of minimum 4 months. Seven of 17 patients (41%) reported an MRC grade ≥ 4 for hallux dorsiflexion. All patients reported improvement of ankle dorsiflexion and sensory changes within one week after surgery.

Broekx et al. (3) described a large retrospective series of neurolysis after excessive weight loss. In total, 200 patients were included and on average patients were operated 4 months after symptom onset. Of all included patients, 85% had a good outcome, defined as an MRC scale for muscle strength grade ≥ 4 for ankle dorsiflexion. Complications after peroneal nerve are unusual(3). In the largest retrospective patient series, 7 out of 200 patients suffered from wound problems, 1 out of 200 patients suffered from postoperative abscess formation and subsequent bacterial sepsis (3). Overall, good outcome after decompressive surgery for peroneal nerve entrapment varies between 43% and 100% in the literature. When interpreting these range of percentages, one should realize that outcome measures differ between the studies. If data was available, good outcome was translated to an MRC-score ≥ 4 for ankle dorsiflexion. If data was not available, outcome measure of the study was documented.

Fares et al. (41) reviewed foot drop after bariatric surgery in 21 cases. Twelve patients were operated and improved (100%). The degree of recovery is often not specified. Table 2 gives an overview of the literature discussed. (Fares et al. was not included in the table, due to the aforementioned reasons.)

Author	**Type of study**	**Number of patients**	**Outcome measure**	**Good outcome (%)**	**Follow-up**
Broekx (3)	Retrospective	200	MRC-score ankle dorsiflexion ≥ 4	85%	N.A.
Maalla (44)	Retrospective	12	MRC-score ankle dorsiflexion ≥ 4	92%	42 months (mean)
Mitra (47)	Retrospective	12	MRC-score ankle dorsiflexion ≥ 4	100%	11 months – 7 years
Lale (57)	Retrospective	9	MRC-score ankle dorsiflexion ≥ 4	100%	Until recovery, max. 60 days

Ramanan (50)	Retrospective	10	MRC-score ankle dorsiflexion ≥ 4	40%	2 – 60 months (mean 19 months)
Wilson (58)	Retrospective	14	Improvement of ankle dorsiflexion	71%	29 months (median)
Nirenberg (56)	**Prospective***	17*	MRC-score ankle dorsiflexion ≥ 4	41%	Minimum 4 months
Tarabay (55)	**Prospective**	14	MRC-score ankle dorsiflexion ≥ 4	86%	1 year

Table 2 Outcome after surgical treatment. *Inclusion of patients with peroneal neuropathy of mixed etiology.

Comparative studies or randomized controlled trials are not available in the literature. Hence, the foot drop trial will be the first, randomized controlled trial to compare both conservative treatment and surgery in a prospective manner.

2 RATIONALE

The rationale for this study is to explore whether a surgical approach to peroneal nerve entrapment is warranted i.e. **does a foot drop, caused by peroneal nerve entrapment, recover faster and better after surgical release?** This question is relevant, given the fact that the actual treatment strategy varies greatly between and even within different centers, depending on the consulting physician.

Since peroneal nerve entrapment represents one of the most common entrapments, and no practice guidelines exist on its preferred treatment, this prospective study will provide important outcome data after conservative treatment (current data very limited), as well as surgical treatment (current data very biased, retrospective in nature and uncontrolled). The impact on quality of life will be assessed and the complications (surgical, chronic pain, sensory changes, …) of both treatments will be recorded. These data will define future treatment guidelines for this mononeuropathy and is thus relevant for all physicians treating entrapment neuropathies (neurology, neurosurgery, physical medicine, orthopaedic surgery, …).

There is indeed insufficient data in the available literature to make any recommendations. No studies have compared surgical versus conservative treatment in a prospective manner and currently no guidelines are available. Even data on the prevalence and the spontaneous evolution of peroneal neuropathy are virtually non-existent.

The lack of prospective studies on this topic is remarkable since most patient series on both the conservative and surgical treatment are retrospective in nature. Most patient series are very heterogeneous given the fact that patients with peroneal nerve damage due to different causes were included, which makes it difficult to draw conclusions on the clinical management. Based on the current literature, the percentage of patients with good outcome after conservative treatment varies between 53% and 100% (9, 22, 24, 28, 36-40). Data concerning the spontaneous evolution of peroneal nerve entrapment (without any intervention) is almost absent, except for 15 patients (28, 41). Furthermore, studies discussing prevalence, report contrasting percentages (7-9).

After reviewing the current literature, we identified several methodological issues when comparing the various studies. Good outcome was not uniformly defined and duration of follow-up differed not only between, but even within studies (where follow-up could range from 5 months to 3 years (36)). Additionally, the number of patients was low to very low in most studies.

Most studies on decompressive surgery for the treatment of peroneal entrapment were retrospective in nature and for most studies the sample size was small. Similar to the studies on the conservative treatment, they involved a heterogeneous patient population and variable follow-up durations. The percentage of patients with good outcome varied between 40% and 100% (see Table 2). A meta-analysis of 136 patients (58) undergoing neurolysis demonstrated that surgery after more than 12 months of symptoms was associated with poorer outcomes, however there was no difference in outcome between surgery before and after 6 months of symptom onset. Overall, patients in the included studies were operated on average 4.6 months after the onset of symptoms (average ranging between 1 month and 27 months). This seems quite late since several authors propose an early release (1, 3, 50, 57), although a recommendation on the exact time interval between onset of treatment and intervention is lacking.

Overall there seems to be a tendency towards better outcome after surgery although this has to be cautiously interpreted. Indeed, no direct comparison between the two treatment modalities exists and most likely, certain surgical patients could have recovered spontaneously as well.

The literature, mostly the lack of it, reflects the current practice in Belgium and the Netherlands. Current practice varies greatly between (and even within) centers. Treatment is mostly based on the personal experience of the physician. Many centers tend to follow a conservative treatment, while other centers tend to operate these patients after varying time windows. This issue became very apparent when different physicians were asked to participate in the trial. Responses ranged from *'We unfortunately cannot participate to the study because we do not operate on patients with a peroneal nerve entrapment. We think it would not be ethical to start performing surgery on these patients'* to *'We want to participate to the trial,*

but we do not want to randomize patients with a foot drop after weight loss. These patients should always be operated on, as soon as possible, and it would therefore not be ethical to refrain from surgery'.

Patients were involved in the trial design and were interviewed for feasibility reasons as well. In total, 31 patient interviews were conducted. These interviews were conducted in a very biased population, given the fact that all patients had undergone surgery. Nevertheless, **74% of patients would be willing to participate in the proposed trial.** The most frequent reason to refuse was related to their profession. Many patients needed to be able to walk safely and often (for example a construction worker). They feared that, if they were not operated on, recovery would take longer, and they would not be able to return to work. Taking this bias into account, 74% of inclusions represents a substantial number. In 90% of patients, the **success of treatment could be measured by improvement in gait**. For 74% good outcome was considered as being able to walk long distances (either for professional or recreational purposes). In 16% of patients, a decrease in frequency of falling was essential for their recovery.

In conclusion, there are various good reasons to conduct the FOOT DROP trial:

1. The optimal treatment for peroneal nerve entrapment (the most common neuropathy in the lower limbs) is unknown. The foot drop trial compares both treatment modalities in order to establish the optimal treatment. This will allow for the development of future guidelines.
2. Impact on quality of life and health economics will be assessed.
3. Useful prospective data, including long-term follow-up data on both treatment modalities will be gathered. Both treatment modalities are considered standard of care at the moment.
4. The study has potential for return on investment, in terms of QALYs, by reducing the number of surgeries (if conservative treatment deems favorable) or by reducing the costs of failed conservative treatment (foot-ankle orthosis, physiotherapy, medications, …)

3 ASSESSMENT AND MANAGEMENT OF RISK

The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

Therefore, this trial is categorised as a low intervention clinical trial.

The risk of adverse events occurring as a consequence of the intervention in this trial is unlikely, therefore safety reporting will be limited to the safety reporting that is necessary in routine care.

4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

4.1 Primary objective

The primary research question of the trial is to assess whether foot drop, caused by peroneal nerve entrapment in adult patients* recovers better within 9 months after decompressive surgery compared to prolonged standard conservative treatment.

* Exclusion of iatrogenic or traumatic peroneal nerve palsies. Exclusion of peroneal nerve compression caused by cysts or tumours. Exclusion of patients with polyneuropathy. Exclusion of other surgical techniques than neurolysis.

Intervention A: Decompressive release of the peroneal nerve at the level of the fibular head in patients with foot drop due to peroneal nerve entrapment.

Intervention B: Prolonged conservative treatment of foot drop due to peroneal nerve entrapment.

Null hypothesis: There is no difference in recovery of foot drop due to peroneal nerve entrapment after intervention A or intervention B.

Alternative hypothesis: Recovery of foot drop due to peroneal nerve entrapment is superior after intervention A compared to intervention B.

4.2 Secondary objectives

The secondary objectives of the foot drop trial are:

- To collect pathology-related data in peroneal nerve entrapment.
- To evaluate and compare quality of life data of patients with foot drop due to peroneal nerve entrapment and to assess the evolution of quality of life during conservative/surgical treatment
- To assess and compare follow-up electrophysiological data in patients with peroneal nerve entrapment
- To assess the evolution of gait impairment in patients with foot drop due to peroneal nerve entrapment through a broad range of questionnaires/gait assessments.
- To assess long-term follow-up (18 months after randomization) data after cross-over is allowed (to collect prospective data on long term follow-up).
- To evaluate the cost-effectiveness of both treatment strategies.

4.3 Endpoints

4.3.1 Primary endpoint

The primary endpoint is the difference in distance covered in meters during the six-minute walk test (6MWD) between baseline and 9 months after randomization. Based on a literature analysis and patient feedback on the trial design, gait analysis and recovery of a normal gait pattern are crucial in the recovery of foot drop. In 88% of interviewed patients, success of treatment was related to gait improvement. The distance covered during the six-minute walk test (6MWD) is validated and clinically used in gait analysis.

4.3.2 Secondary endpoints

Key secondary endpoint: time to recovery.

Very limited data is available regarding time to recovery after surgical or conservative treatment in peroneal nerve entrapment (35, 55). Time to recovery is defined as: the time necessary to cover the minimal age- and sex-specific normal 6MWD AND the time necessary for foot drop recovery to an MRC-score ≥ 4 for ankle dorsiflexion. The minimal age- and sex-specific normal 6MWD is defined as 82% of the applied reference equations for prediction of the 6MWD (59, 60). The reference value that will be used is $6MWD_{pred}(m) = 868.8 – (age_{years} \times 2.99) – (gender \times 74.7)$. The value for gender is 0 in male subjects and 1 in female subjects (60).The reference values and equation are added to the study protocol in Appendix 5.

Other Secondary outcomes

1. **Ankle dorsiflexion strength:** measured by the MRC-score and isometric dynamometry at 10 days, 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Ankle dorsiflexion strength will also be assessed after 10 days in the surgical arm of the trial.
2. **Gait assessment** at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization with
    a. Functional ambulation categories, Stanmore questionnaire
    b. Gait speed during the 10-meter walk test
    c. The proportion of patients in both groups who reach minimal normal age- and sex-specific reference values for 6MWD, 9 months after randomization.
    d. Difference in distance covered in meters during the six-minute walk test between baseline and 6 weeks, 3 months, 6 months and 18 months after randomization
3. **Complications and neurological deficits** :
    a. Motor changes including MRC-score for ankle eversion and hallux extension at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Motor function will also be assessed after 10 days in the surgical arm of the trial.
    b. Sensory changes at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Sensory changes will also be assessed after 10 days in the surgical arm of the trial.
    c. Surgical complications at 10 days, 6 weeks and 18 months after surgery: a list of possible complications is composed to score in a uniform way in all centers.
4. **Health-economic assessment:**
    a. Work productivity and Activity Impairment Questionnaire at 6 weeks and 6 months after randomization.
    b. Return to work at 6 weeks after randomization.
5. **Electrodiagnostics (EDX)** at 3 months and 9 months after randomization.
6. **Patient-reported outcome measures:** health-related quality of life (EQ5D-5L) at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization. Patient-reported outcome measurements will also be assessed after 10 days in the surgical arm of the trial.

For all secondary endpoints, baseline measurements will be obtained if applicable.

5 TRIAL DESIGN

5.1 Full-scale study design

The overall objective of the foot drop trial is to test the superiority of surgical release of the peroneal nerve at 10 +/- 4 weeks after symptom onset to maximal conservative treatment. The FOOTDROP trial is designed as a prospective, multicenter, randomized, parallel-design study. A double-blind design is not possible, given the fact that both the treating physician and the patient will always know the allocated treatment strategy. The clinical researcher (= outcome assessor) will be blinded for treatment.

Subjects will be randomized 1:1 to surgery or conservative treatment (simple randomization based solely on a single, constant 1:1 allocation ratio). If a patient, that signed the informed consent form (ICF), cannot be randomised because the foot drop has recovered, this will be documented in the eCRF. After randomization, the patients allocated to conservative treatment will enter a treatment period of approximately 9 months (individualised physiotherapy program). Patients allocated to the surgical arm will undergo surgery as soon as feasible after randomization (maximum within 1 week, preferably within 2 days). For all participating patients that signed the informed consent at the screening visit, an operation day will be scheduled, maximum one week after the randomization visit (due to practical scheduling reasons). At the moment of scheduling, the patient will be unaware of this date to prevent bias (and orientation of the mindset of patients toward surgery). If a patient is allocated to the conservative arm of the trial, the scheduled operation date will be cancelled, without knowledge of the patient. To facilitate signing of the informed consent form at the screening visit, patients will be informed prior to the consultation about the study (by telephone, through the patient brochure).

Patients in the surgical arm of the trial, are allowed to follow physiotherapy after surgery. The frequency and intensity are to be determined by the treating physician. All participants are allowed to use an ankle-foot orthosis. The use of electrostimulation is not advised, although not forbidden.

The endpoints will be evaluated at fixed time-points: 6 weeks, 3 months, 6 months and 9 months after randomization. Extended follow-up is scheduled 9 months after the primary endpoint is reached i.e. 18 months after randomization. Most trial assessments will be performed by the site-specific blinded researcher, ideally an independent physiotherapist. Patients allocated to the surgical arm of the trial will be evaluated 10 days after neurolysis. A postoperative control is considered standard of care. Sensorimotor function, quality of life and complications will be assessed during this postoperative control. Assessment of MRC-scores for ankle dorsiflexion and ankle eversion is considered standard of care and shall be performed by the treating physician. The treating physician can also assess ankle dorsiflexion strength measured by isometric dynamometry. This cannot be done by the outcome assessor because this would lead to unblinding.

A list of standard assessments (clinical records, considered daily practice = SOC; including motor and sensory function, ability to walk (barefoot), need for orthosis, treatment) will be composed for uniformity across centers. Standard assessments will be conducted at each study visit.

Cross-over is not allowed until the primary endpoint at 9 months is assessed. After the primary endpoint is assessed, cross-over from the conservative arm to surgery is allowed and patients will be treated according to standard of care (decision between treating physician and patient). Extended follow-up for all patients will be organised, 18 months after randomization. All primary and secondary endpoints, with the exception of electrodiagnostics, WPAI and return to work, will be assessed at 18 months. The End-of-Study (EOS) visit will take place at 18 months post-randomization. Cross-over patients will be followed-up as per protocol. All participating physicians and trial sites have the responsibility to guide patients throughout the study visits and are expected to follow protocol and to inform patients in a correct, objective manner. If the TSC documents an unusual high percentage of cross-over in a specific trial site, this trial site can be excluded from the foot drop trial.

Ninety-one patients will be enrolled in each arm of the trial, so that in total 182 patients will be enrolled in the foot drop trial. A blinded sample size reassessment by the trial statistician is planned when 50% of the planned patients have reached their 9 month visit or one month before the final patient would be

randomized, whichever occurs first. A dropout rate of 5% is anticipated, based on a large randomised trial with similar design (61, 62).

The foot drop trial is a multicenter trial. The number of participating centers will vary in function of the recruitment rate. In a first phase, 14 additional centers will be initiated apart from the pilot study centers. If recruitment is slower than expected, an additional 6 centers can be initiated. In other words; the study will run in 20 to 26 centers in Belgium and the Netherlands. The number of Dutch centers will be limited to 4 (phase 1 + phase 2).

Subgroup analysis

A literature search was performed to identify predictors of good and bad outcome after surgical or conservative treatment. There is only limited data available and the data discussed come from several retrospective patient series (3, 38, 39, 43, 44, 63), one prospective conservative multicenter trial (28), one prospective case series (40) and one meta-analysis (58). Based on the cited articles, the following predictors of outcome will be used for further analysis:

1. Diabetes
2. Smoking (No, history, current)
3. Rapid/significant weight loss (> 5% of total body weight (18, 64))
4. High age (> 60 years)
5. Prolonged squatting

These predictors will be used in an exploratory analysis for the primary and key secondary endpoint (see Section 11). In this way, interactions between the predictor and a possible treatment effect can be identified and several new hypothesises can be generated to be investigated in further trials (were several subgroups could be studied in further detail).

-

6 STUDY SETTING

The foot drop trial is a multicenter study.. In function of the recruitment rate, up to 23 Belgian centers and 5 Dutch centers will participate in the trial.

In each participating centre, there should be a department of neurosurgery, neurology and physical medicine/rehabilitation. The departments of orthopaedic surgery and plastic and reconstructive surgery will be involved as well if they are routinely involved in this patient care. To accentuate the multidisciplinary collaboration throughout the study, an non-surgical adjunct principal investigator should be appointed in each centre. There needs to be at least one neurologist/rehabilitation physician that is thoroughly trained in electrodiagnostics and has experience with the interpretation of electrophysiological investigations in patients with peripheral nerve entrapment. Since all patients are diagnostic using electrodiagnostics, the adjunct principal investigator is preferably the local electrophysiologist.

The surgical procedure is not considered very complex. Therefore, every general neurosurgeon is qualified to perform the procedure in participating patients. A neurolysis can also be performed by an orthopaedic surgeon with experience in peripheral nerve surgery. Preferentially, every participating centre has an experienced peripheral nerve surgeon. The rehabilitation program can be organised within the participating center or in an ambulant setting, with physiotherapists working according to the proposed guidelines (designed to be a mirror of current daily practice).

The blinded researcher (or outcome assessor), can be a site-specific clinical trial assistant, study-nurse, physiotherapist, resident or other qualified medical professional. The blinded assessor is preferably an independent physiotherapist. At each participating site, the (blinded) researchers will be trained in certain clinical assessments including isometric dynamometry and MRC-scoring for ankle dorsiflexion, hallux extension and ankle eversion. Training videos will be made available, so that a uniform assessment can be made in the different centers and inter-observer variability can be reduced to the minimum. These training videos will be shown at the site initiation visit and will be accompanied by a questionnaire. In this way, it can be guaranteed that the training has been followed.

The majority of patients with peroneal nerve entrapment and foot drop present in an emergency setting. Most often, these patients are referred by general practitioners because of sudden gait difficulties and an increased risk of falling. Sometimes the reason for referral is further diagnostics since foot drop has a broad differential diagnosis, and some diagnoses require (semi-)urgent treatment (for example L5 radiculopathy with foot drop due to lumbar disc herniation). In other cases, patients present at the emergency department without referral because of the paralysis of the foot and associated gait difficulties. A small group of patients presents in private clinics of neurologists and physical medicine and rehabilitation physicians. With the exception of some unique cases, almost all patients present in the acute setting. The first medical examination is almost never conducted more than three months after onset of symptoms. The statements above are based on experience and conducted patient interviews.

In every peroneal nerve entrapment case, diagnosis is made at the electrophysiology department. Involving the local electrophysiologist is therefore key to trial success. Ideally, the local electrophysiologist should be appointed as the non-surgical adjunct principal investigator.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

For inclusion in the study, the subject must fulfil the following inclusion criteria:

- Written informed consent to participate in the study must be obtained from the subject or proxy / legal representative prior to initiation of any study-mandated procedure
- EDX-documented peroneal nerve entrapment with persisting (10 ± 4 weeks) foot drop (MRC-score ≤ 3)
- Imaging (ultrasound/MRI) performed to exclude a compressive mass
- Age ≥ 18 years

7.2 Exclusion criteria

- Subjects with posttraumatic or iatrogenic peroneal nerve injury
- Subjects with peroneal neuropathy due to a compressive mass (e.g. cyst, tumour)
- Peroneal nerve entrapment at other sites than the fibular head
- Bilateral peroneal nerve entrapment
- Patients with mental or physical problems that incapacitate them to participate in a physiotherapy program
- Psychiatric illness
- Pregnancy
- Planned (e)migration within 1 year after randomization to another country
- Subjects with previous foot drop
- Permanently bedridden subjects
- Subjects with neurological or musculoskeletal history which could impact foot drop assessment and/or gait analysis (e.g. polyneuropathy, hereditary neuropathy with pressure palsies, critical illness polyneuropathy, previous stroke, ankle surgery, ankle sprain, …).

8 TRIAL PROCEDURES

8.1 Recruitment

All patients with foot drop due to peroneal nerve entrapment will be screened for eligibility at the screening visit. If a patient does not meet the inclusion criteria, or if a patient declines to participate, this will be documented in the screening log (ineligibility). Reasons for refusal to participate will also be documented in the screening log. Data will be anonymised. If a patient does not receive the allocated treatment after randomisation, the reason will be documented in the screening log and the reason will be communicated to the trial co-ordinator. In summary, the following information will be collected in the screening log:

- Screening number (not allowed to use initials, patient identification codes, not allowed to use any combination of elements that might allow the patient to be identified (GDPR)
- Date of consent (if applicable)
- Version of consent (if applicable)
- Date screened
- Eligible for enrolment?
- Study specific number (only to be completed for enrolled subjects)
- Date of randomization (if applicable)
- Ineligibility reasons (if applicable). If a patient enrolled in the study but cannot be randomized due to recovery, this will be clearly documented.

This allows for data collection in accordance with the 2010 CONSORT statement (Consolidated Standards of Reporting Trials) (65).

8.1.1 Patient identification

Most patients, if not all, present within 3 months, due to the acute onset of paralysis. A significant percentage of patients with foot drop is referred (by the general practitioner) to the emergency department and will be detected in a very early stage. The reason for early referral is caused by the functional deficit resulting in difficulties walking and also due to the fact that the differential diagnosis of foot drop is broad, and certain diagnoses require urgent treatment. Other patients will seek medical attention without referral because of sudden gait problems. All but one interviewed patients sought medical attention within six weeks after the onset of symptoms, 63% presented in the first week.

The patient will be seen by a neurosurgeon, an orthopaedic surgeon, a neurologist or a physical medicine doctor. These departments will thus be heavily involved in this trial. . In every peroneal nerve entrapment case, diagnosis is made at the electrophysiology department. Involving the local electrophysiologist is therefore key to trial success. Ideally, the local electrophysiologist should be appointed as the non-surgical adjunct principal investigator.

The treating physician will recruit the patient. At this stage, only the existing clinical care team has access to the patient records and therefore the treating physician will evaluate if the subject is a suitable candidate for the study based on the inclusion and exclusion criteria. There will be no recruitment through publicity (posters, leaflets, adverts or websites). Patient or disease registers will not be used to identify potential participants.

A small percentage of patients with foot drop due to peroneal nerve entrapment will present to neurologists and rehabilitation physicians in private practice, who do not always refer these patients to hospitals or surgical departments because they prefer a prolonged conservative treatment. An informative letter about the foot drop trial will be made to sensitize this group of treating physicians to refer their patients to a participating centre. These letters will be distributed through the representative national societies of both

specialisations. Furthermore, a manuscript reviewing the literature on peroneal nerve entrapment and discussing the foot drop study design was published in TNN (Tijdschrift voor Neurologie en Neurochirurgie).

8.1.2 Screening

Peroneal nerve entrapment will be confirmed by EDX after clinical investigation which is standard of care. The electrodiagnostic protocol will include motor nerve conduction studies [nerve conduction velocities, distal motor latencies, amplitudes of compound motor action potentials (CMAPs)], sensory nerve conduction studies and electromyography (EMG) evaluation during rest and voluntary contraction. EDX can identify other neuropathies/polyneuropathies or entrapment at other sites than the fibular head

Imaging (MRI or/and ultrasound) will be performed to document a compressive mass at the level of the fibular head (cysts/tumours). Through patient history and clinical investigation, the treating physician can identify posttraumatic or iatrogenic nerve injury, as well as subjects under the age of 18 years, previous foot drops and permanently bedridden patients. Eligibility screening procedures involve no investigations that emit ionising radiation. A knee X-ray is optional and warranted in traumatic peroneal nerve injury, but these patients are excluded. In a traumatic peroneal neuropathy, an x-ray of the knee is considered standard of care.

After the diagnosis of an EDX confirmed peroneal nerve entrapment at the level of the fibular head is made, the patient can be considered for inclusion in the trial, provided that ICF is obtained, and all other in- and exclusion criteria are fulfilled.

After the ICF has been signed, the local investigator or delegate contacts the clinical coordinator to allocate a subject number to the subject.

There are no intended payments to participants except reimbursement of reasonable travel expenses for any visits additional to normal care and reimbursement of expenses of extra investigations. There will be no extra payments to avoid a financial incentive to participate in the trial. Details on the amount of payment will be included in the informed consent form.

8.2 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site. Data can only be collected if informed consent form is signed at the screening visit. In daily practice, this is often not the case since patients want to overthink participation. Throughout the pilot study, several patients that were willing to participate but recovered before informed consent form was signed. This data is lost.

To tackle this issue, we will train and encourage centers to contact patients about the study prior to the study visit by telephone. Information about the trial is given and the patient brochure is sent to the patient. In this way, patients are already informed about the study at the screening visit and informed consent form can be signed.

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

The participant population is not likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment (the patient must be a suited candidate for physiotherapy in order to participate in the trial). However, if present, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant's behalf (in the case of problems with reading or writing), designate a legal representative, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment) providing they are approved by the Ethics Committee (EC).

Informed consent will be signed by the patient or a legal representative. In the foot drop trial, the ICF will be discussed and signed at the screening visit. This process will involve:

- discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research, the nature and objectives of the trial and possible risks associated with their participation
- the presentation of written material (e.g., information leaflet and consent document which must be approved by the EC and be in compliance with GCP, local regulatory requirements and legal requirements)
- the opportunity for potential participants to ask questions
- assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
    - understand the purpose and nature of the research.
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens.
    - understand the alternatives to taking part.
    - be able to retain the information long enough to make an effective decision.
    - be able to make a free choice.
    - be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).
    - where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected.

General good practice in research (and the basis of legal frameworks) require that persons incapable of giving legal consent should be given special protection.

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. In practice for participants with mental incapacity this means that they should not be included in clinical trials if the same results can be obtained using persons capable of giving consent and should only be included where there are grounds for expecting that their taking part will be of direct benefit to that participant, thereby outweighing the risks.

If subjects, who lacks the capacity to consent for themselves, are considered for inclusion, the PI should determine if the patient is incapacitated to participate in a physiotherapy program. If not, the patient is not suited to be included in the trial (inclusion and exclusion criteria).

Where a participant is able to consent for a clinical trial but later becomes incapacitated (for example progressive cancerous disease), in all such cases the original consent given endures the loss of capacity,

providing that the trial has not significantly altered and the patient can continue the physiotherapy program. If cessation of any further clinical intervention or follow-up is mandatory, patients will be analysed according to the intention-to-treat principle (i.e. all patients randomized included in the analyses and analysed in the group to which they were randomized).

8.3 Trial randomisation

Trial randomization is mandatory and affords an unbiased comparison between groups as it controls for both known and unknown variables. Through randomization both the conservative and surgical treated group will be balanced regarding prognostic variables. Both treatment groups will be prognostically balanced (with exception of the intervention), so that if a difference in outcome is observed, a sound argument can be made attributing the difference in result to the intervention under study. Simple randomization based solely on a single, constant 1:1 allocation ratio will be used in the foot drop trial.

The Randomization Module within REDCap will be used to assign participants to specific groups (web-based randomisation/treatment allocation system). In this way, an unpredictable allocation sequence will be generated so that the treatment allocation is concealed from the randomizing treating physician. Randomization will be documented by e-mail. Since peroneal nerve entrapment is not a medical emergency, randomization will not be done outside of the office hours. Randomization will not be stratified by centre because of the risk of selection bias due to treatment predictability in centers with low inclusion rates. Furthermore, due to the anticipated low inclusion rate in several centers, an imbalance in the number of patients per study arm can be created when working with stratification by centre. Therefore, randomization will be global over all participating centers. The PI of the local centre, as well as all the treating physicians, and the study coordinator will receive User Rights for the Randomization Module. The study coordinator should have an overview of all the randomizations made in each centre.

8.4 Blinding

Blinding of trial participants and care providers is not possible because of obvious differences between both treatment groups: one group will be surgically treated whereas the other group will receive maximal conservative treatment until the primary endpoint is assessed. However, the clinical investigator in the foot drop trial (= outcome assessor) can be blinded to treatment. All participants will be asked to wear long trousers to cover a potential scar at the level of the knee. Furthermore, all patients will be asked to apply a bandage at the site of the operation (or the site of entrapment if there was no operation). Participants are not allowed to discuss their treatment with the outcome assessor. A preassessment contact between the patient and an unblinded member should be organized prior to the study assessments, to remind and instruct patients of the blinding precautionary measures.

Patients in the surgical arm of the trial will be evaluated after 10 days. A postoperative control is considered standard of care. Assessments cannot be performed by the outcome assessor at this stage, as this will cause unblinding.

Since all health care providers have access to the electronic health record, measures should be taken to prevent unblinding of the outcome assessors. Several precautions should be considered:

- Data of assessments will be documented on a separate worksheet, outside the electronic health record so that there will be no need to access the electronic health record.
- If the outcome assessor thinks the electronic health record should be accessed, the treating physician should be consulted. Since the treating physician is not blinded, he/she can access the electronic health record if deemed necessary.

To avoid errors, the outcome assessor must be aware of the identity of the patient during the assessments. Therefore, anonymization during assessment is not possible.

Blinding the outcome assessor will create the opportunity to make an objective assessment of primary and (key) secondary outcome parameters, without increasing the risk of bias.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential. The randomization list is accessible only by the REDCap data manager to prevent further selection bias. The statistician should neither have access to randomized treatments (or randomization list) nor even to the full database until the database has been locked for analysis.

8.5 Unblinding of outcome assessor

Full randomization information will be made available for data analysis only after database lock. Given the fact that both the care providers and patients aren't blinded, situations that require unblinding of the outcome assessor during the trial will be rare. Surgical complications can occur in the postoperative period, during which the patient is followed by the treating physician. In situations where the patient signals treatment related problems during the examination by the outcome assessor, the treating physician should be consulted. The treating physician, who is not blinded can assess the problems of the patient and can decide if unblinding of the outcome assessor is necessary. Where possible, the outcome assessor should remain blinded.

Accidental unblinding of outcome assessors can happen. Measures will be taken to anticipate the occurrence of such event. A preassessment contact with an unblinded member of the study team will be scheduled prior to the study visit, to remind patients of the blinding and help them with placing the bandage or other blinding material. In all participating centers, at least 2 outcome assessors should be trained and deployable. In case of accidental unblinding of one outcome assessor, the other outcome assessor can follow-up on the particular patient during the remaining study visits.

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. In the foot drop trial, these situations will be virtually non-existent, since the treating physician is not blinded.

The occurrence of any emergency unblinding during the study must be clearly justified and explained by the investigator. In all cases, the sponsor personnel must be informed about the reason for unblinding as soon as possible before or after the event. The circumstances leading to unblinding must be documented in the hospital charts, the Investigator Site File (ISF) and in the eCRF. If unblinding occurs, all assessments as defined in the study protocol must still be performed, unless the subject withdraws consent to participate in the study.

8.6 Baseline data

Baseline data can be collected by the treating physician during the **screening visit** and will be recorded in the eCRF.

- EDX characteristics (see also 8.7.2.)
- Sex (male/female)
- Height in centimetres
- Age in years
- Site of entrapment (left/right/bilateral)
- Time since onset of foot drop in weeks
- MRC score for ankle dorsiflexion and ankle eversion at presentation
- Subacute onset (>2days) of foot drop
- Weight loss during last 6 months:

    - Weight loss in kg
    - Current weight
    - BMI (kg/m^2)
    - Is weight loss intentional?
    - Weight loss after bariatric surgery?
    - Rapid onset?
- Postural neuropathy
    - Habitual leg crossing?
    - Prolonged squatting?
    - Frequent kneeling?
- Exercise (dynamic compression)
- Onset after childbirth?
- Previous lumbar surgery?
- Trauma
    - Sharp/blunt
    - Inversion trauma of the ankle
    - Knee dislocation
    - Other
- Iatrogenic causes of peroneal neuropathy
    - Surgery of the hip/knee/ankle
    - Other surgery (e.g. wrong positioning during thoracic surgery)
    - Recent bracing/ pneumatic compression device/ compression wrapping
    - Other
- Metabolic/systemic disease
    - Diabetes mellitus
    - Thyroid disease
    - Vitamin deficiencies e.g. B12
    - Oncological history
    - Other
- Prolonged bedrest
- Professional occupation
- Use of alcohol in units/week
- Tinel sign at the level of the fibular head
- History of neuromuscular diseases
- Professional disability
    - Currently employed/working?
    - Ability to continue working? (last day of work if the patient is unable to work)

Baseline assessment for the primary and secondary endpoints analyses will be collected at the **randomisation visit** by the **outcome assessor** (blinded researcher), this will reduce inter-observer variability during follow-up. The limited baseline assessments conducted by the treating physician should be conducted before the actual randomization to avoid bias. The EQ5D-5L is only to be registered if the patient did not complete the online survey or if the patient chose to not use the online system.

Baseline primary and secondary endpoint data will include:

- MRC-score for ankle dorsiflexion, hallux extension and ankle eversion
- Gait assessment:
    - **Distance covered during the six-minute walk test (primary outcome)**
    - Gait speed during the 10 meter walk test
    - Ability to walk barefoot
    - Stanmore questionnaire
    - Need for foot-ankle-orthosis
    - Functional ambulation categories
- Sensory changes
- Quality of life questionnaire
    - EQ-5D 5L
- Work and Productivity Impairment Questionnaire (WPAI)

8.7 Trial assessments

In the section below, all study procedures and trial assessments are described, as well as their timing. Several assessments will be performed by the treating physicians, others by the outcome assessor (blinded researcher). The study assessments are listed in the visit and assessment schedule (see Section 8.8).

A list of standard assessments (clinical records, considered daily practice; including motor and sensory function, ability to walk (barefoot), need for orthosis, treatment) will be composed for uniformity across centers. These data will be collected at every study visit and will be recorded in the eCRF. The list of standard assessments is included in appendix 4.

Several questionnaires (EQ-5D 5L, WPAI) will be made available as an online survey (REDCap) for patients. All other questionnaires completed by the subject or proxy are entered into the corresponding eCRF form by the study coordinator. The original paper copies of the questionnaires that are not available online will be filed in the ISF and made available for verification by the site monitor. If patients fail to complete the survey online, the blinded researchers can make sure that the questionnaires are complete during follow-up. If the patient is unable to return to the investigative site for study specific follow-up, the questionnaires will be sent to the patient's home (and the clinical evaluation will be recorded as missing data). Patients will receive a message prior to each evaluation moment, to remind them of the upcoming assessments. At every assessment, the schedule of the assessments to come will be discussed with the patients as an extra reminder.

If visits or data collection time-points are missed, despite previous mentioned efforts, following measures will be taken:

- The outcome assessor will inform the treating physician, PI, clinical trial assistant or any other non-blinded study personnel. The patient will be contacted to reschedule the visit as soon as possible. This cannot be done by the outcome assessor to guarantee blinding.
- If the patient is not able to reschedule, the reason will be documented in the eCRF. If possible, certain assessments will be evaluated through telephone:
    - EQ-5D 5L questionnaire

    - WPAI questionnaire
    - Sensory changes
    - Ability to walk barefoot
    - Need for foot-ankle orthosis
    - Return to work
    - Registration of treatment
- The scheduling of the following appointments will be checked with the subject, to be sure that further follow-up is guaranteed.

The site and study team must take preventive measures to avoid a subject being lost to follow-up (at least 3 contacts (e.g., telephone calls or e-mails) must be placed to the last available telephone number or e-mail address) and 1 registered letter must be sent by post to the last available home address. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If a patient decides to not attend to some follow-up visits (for example a patient with fast recovery after surgery), efforts should be made to convince the patient to agree to the study visit at 9 months after randomization. The visit at 9 months is the most important study visit due to assessment of the primary endpoint. In this way, the patient is not lost to follow-up and the other visits will be marked as 'missed data collection time-points'.

For protocol non-adheres, all endpoints will be assessed according to protocol if the patient chooses to remain included in the trial.

8.7.1 Time to recovery

Limited data are available in the literature regarding time to recovery after surgical or conservative treatment in peroneal nerve entrapment (35, 55). Time to recovery is defined as: the time necessary to cover the minimal age- and sex-specific normal distance in meters during the six-minute walk test AND the time necessary for foot drop recovery to an MRC-score ≥ 4 for ankle dorsiflexion. The minimal age- and sex-specific normal 6MWD is defined as 82% of the applied reference equation for prediction of the distance covered in the six-minute walk test (59, 60). The reference value that will be used is $6MWD_{pred}(m) = 868.8 – (age_{years} \times 2.99) – (gender \times 74.7)$. The value for gender is 0 is the patient is male and 1 if the patient is female (60) .The reference values and equation are added to the study protocol in Appendix 5.

The reference equation of Gibbons et al. is used, because this is based on the 6MWD in healthy Caucasian patients aged between 20 and 80. Troosters et al. stresses the variability in 6MWD in a healthy population and therefore proposes to consider a 6MWD smaller than 82% of the predicted 6MWD as abnormal (59). The reference equation proposed by Troosters et al. is not used, despite the inclusion of Belgian healthy subjects, due to the fact that no patients younger than 50 years old were included in this trial. However, the average difference between the predicted 6MWD derived from the study of Troosters et al. and predicted 6MWD according to Gibbons et al. was only 8.8 meters (standard deviation 73.6 meters) (60). Other publications on reference values of 6MWD in healthy subjects were discarded because of inclusion of restricted age categories (66-69) or different ethnic groups (70, 71).

8.7.2 Electrodiagnostics (EDX)

Electrodiagnostic testing will be performed at baseline (screening visit, standard of care). After randomization, EDX will be repeated after 3 months and 9 months. EDX will be conducted by a trained neurologist/rehabilitation physician (see Section 6. Study Setting). EDX after randomization is not considered standard of care. The diagnosis of peroneal nerve entrapment is based on the screening EMG and falls outside the scope of the trial. However, electrophysiologists in the participating centers are advised to follow the 'guidelines' below.

In 2005, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) published a practice parameter for the use of EMG (electromyography) and NCS (nerve conduction studies) in evaluating patients with peroneal neuropathy (72), based on a thorough review of the literature. These recommendations however were based on Class III and IV evidence and classified as level C recommendations, reflecting the paucity of the literature on this topic (72, 73). Nevertheless, EDX was considered useful in making and/or confirming the diagnosis of peroneal neuropathy and in providing prognostic information. Following recommendations for electrodiagnostic techniques for diagnosing peroneal neuropathy were formulated:

- Peroneal motor NCS with assessment of conduction velocity through the fibular head and in the leg with recording from the anterior tibial (TA) muscle and extensor digitorum brevis muscle (EDB).
- Orthodromic and antidromic superficial peroneal sensory NCS
- At least one additional motor or sensory NCS in the same limb with normal findings (expert opinion)

The role of needle EMG in making a diagnosis remained questionable. However, experts suggest that abnormalities on needle examination outside of the distribution of the peroneal nerve should suggest alternative or additional diagnoses (6, 72).

No limits for abnormality were suggested in the literature, so following criteria were designed based on experience and previous trials in the literature (6, 10, 21, 74-76):

- Difference in motor nerve conduction velocity across the fibular head of more than 10 m/s AND/OR
- Presence of a motor conduction block: delta CMAP (compound motor action potential) amplitude across fibular head > 30%

Furthermore, the presence of and extent of axonal damage and mixed involvement needs to be studied, since these patients are expected to improve later and slower (1, 23).

Following data will be collected in the eCRF (a paper source document is available to the local electrophysiologist):

- Difference in conduction velocity across the fibular head (m/s)
- Motor nerve conduction velocity (proximal and distal to the fibular head)
- CMAP distal motor latency
- Superficial peroneal sensory potential
- Conduction block: drop in amplitude (%)
- EDB-CMAP (in mV) (proximal and distal to the fibular head)
- Rest EMG abnormalities
- EMG during voluntary contraction abnormalities
- Evaluation of axonal damage
- Evaluation of mixed damage

8.7.3 Muscle Power Assessment (Medical Research Council's scale)

The MRC-score is a clinical assessment. A score from 0 to 5 is used to grade the power of a muscle group in relation to the maximum expected for that muscle. The score was first published in a manuscript called *'Aids to the investigation of peripheral nerve injuries' (77)* and has since been used in many clinical trials and publications. The MRC-score is a widely used tool to assess muscle strength in peripheral nerve pathology and used on a daily basis around the world to assess strength of foot dorsiflexion in patients with foot drop. Training videos for the trial investigators will be made available, so the MRC-scoring will be more rigorously applied and inter-observer variability will be reduced a strict minimum. Several modified MRC-scores are available, taking range of motion or more subtle changes in muscle strength into account (78). However, there are several disadvantages in using modified scales. There are more possible measurements and there will be more inter-observer variability. Furthermore, the MRC-score as depicted below is more representative for daily practice.

The MRC score will be noted at every visit:

- Screening visit: treating physician
- Randomization visit:treating physician* and outcome assessor (before, during or after randomization)
- 10 days after surgery: treating physician
- 6 weeks after randomization: outcome assessor
- 3 months after randomization: outcome assessor
- 6 months after randomization: outcome assessor
- 9 months after randomization: outcome assessor
- 18 months after randomization: outcome assessor

** before the actual randomization to avoid bias.*

MRC-score will be determined for ankle dorsiflexion, hallux extension and ankle eversion. Good outcome corresponds to an MRC-score ≥ 4 for ankle dorsiflexion. Assessment of muscle strength using the MRC-score is considered standard of care in the follow-up of patients with foot drop.

Medical research council (MRC) muscle strength	
MRC 0	No muscle contraction
MRC 1	Muscle contraction, no movement
MRC 2	Movement, but not against gravity
MRC 3	Movement against gravity, but not against resistance
MRC 4	Movement against resistance, but not normal strength
MRC 5	Normal strength

8.7.4 Isometric dynamometry

Recovery of ankle dorsiflexion strength is essential in patients with foot drop. The use of dynamometry allows to document ankle dorsiflexion strength in an objective manner. Dynamometry has frequently been used to assess muscle strength in patients with foot drop (79-81). Won et al. (81) used a handheld dynamometer to assess ankle dorsiflexion strength in 52 patients with peroneal neuropathy (47 traumatic peroneal neuropathies and 3 idiopathic peroneal neuropathies). During the foot drop trial, results will be obtained and reported according to the same method.

Patients are asked to lay in a supine position, with the knees extended. The test pad of the dynamometer is placed on the dorsal head of the first metatarsal bone. The patient is instructed to perform ankle dorsiflexion with maximal muscle strength. The best of three attempts is registered. Ankle dorsiflexion is measured and reported for both ankles (in Newton). The ankle dorsiflexion strength ratio, defined as the ratio of ankle dorsiflexion strength in the affected ankle over ankle dorsiflexion strength in the healthy ankle will be calculated and reported in the eCRF. Training videos for the trial investigators will be made available, so that the inter-observer variability will be reduced to a strict minimum.

Based on the experience with isometric dynamometry throughout the FOOTDROP pilot study, following instructions are proposed to collect data in the most uniform way:

1. The ankle joint is placed in neutral position (90°). Aid the patient if necessary. Register the best of three attempts. If a patient is not able to generate any dorsiflexion strength, do not apply resistance, to avoid registering passive resistance.
2. The ankle joint is placed in ‘natural position’. The natural position is defined as the position of the ankle joint in the sagittal plain when the patient is neither actively dorsiflexing of plantarflexing the ankle joint. Since the natural position is depending on muscle tone in both the dorsiflexion and plantarflexion muscles, this is patient (and time) dependent. Register the best of three attempts. If a patient is not able to generate any dorsiflexion strength, do not apply resistance, to avoid registering passive resistance.

3. Register normal strength in both positions at the contralateral healthy site in order to calculate the two relevant ankle dorsiflexion strength ratios (in neutral (90°) and natural position).

The use of isometric dynamometry is not considered standard of care. The treating physician will perform dynamometric measurements at 10 days in the surgical group to avoid unblinding. The blinded outcome assessor will perform dynamometric measurements at baseline, six weeks, 3 months, 6 months, 9 months and 18 months. The MicroFet 2 dynamometer, distributed by ProCare, will be used in all participating centers.

8.7.5 Six-minute walk test (6MWT)

The primary endpoint is the difference in distance covered in meters during the six-minute walk test (6MWD) between baseline and 9 months after randomization. The distance in meters covered during the six-minute walk test at 6 weeks, 3 months, 6 months and 18 months will be recorded as secondary endpoint. Including a six-minute walk test at earlier time points will allow us to assess the 6MWD before any possible cross-over could have occurred. Moreover, a quicker improvement in gait as measured by the 6MWT may also represent an important outcome parameter. Each assessment will be performed by the outcome assessor. Performing the six-minute walk test is not considered standard of care.

Based on a literature analysis and patient feedback on the trial design, gait analysis and recovery of a normal gait pattern are crucial in the recovery of foot drop. In 88% of interviewed patients, success of treatment was related to improvement in gait. The distance covered during the six-minute walk test (6MWD) is validated and clinically used in gait analysis. Several advantages exist in daily practice when using the 6MWT. There is no need for expensive equipment and the test can be performed in every hospital. It is possible to work in a very standardized manner and patient instructions can be easily understood. Since we measure speed and distance over a period of 6 minutes, we get much more information about gait than during a shorter version of the test. It is also possible to detect fatigability. Since we look at differences between baseline values and values after 9 months, the influence of comorbidities (such as age, pulmonary or cardiac problems, …) can be limited.

The 6MWT has been used in other studies examining foot drop due to other pathologies including multiple sclerosis and stroke (32-34, 82-85). Baseline values for these pathologies are therefore available. Unfortunately, direct baseline values from previous trials of patients with foot drop due to peroneal nerve entrapment are non-existent. Moreover, the data available from other trials concerning foot drop due to different pathology are expected to differ from the foot drop trial study population because of the following reasons:

- The available data on foot drop are extracted from a population with either multiple sclerosis or ischemic stroke. These neurological conditions differ greatly from a peripheral, focal neuropathy. In these patients, the neurologic deficits are caused by lesions in the brain resulting in other clinical presentations which are more generalized compared to an isolated foot drop. Our trial will be able to provide better quantitative measures related to foot drop in this patient population. Currently we only have qualitative evidence based on interviews that walking is hampered in patients with foot drop due to peroneal nerve entrapment.
- Based on our review of the literature, we expect large numbers of patients to recover partially or fully after peroneal nerve entrapment, regardless of the treatment modality. Good outcome after surgical treatment varied between 41% and 100% and good outcome after conservative treatment varied between 53% and 100% (see Section 1 and 2). This rate of recovery is different from recovery in patients with multiple sclerosis or stroke.
- Extrapolation of data is further complicated when MS or stroke patients are allowed to use a foot-ankle orthosis during the 6MWT.

Since the 6MWT is a widely used test, reference data about distance covered in the normal population are available (59, 60, 66-71). We can only provide data on healthy subjects which can serve as surrogate

markers for the optimal outcome for patients. As mentioned before (see Section 8.7.1: time to recovery), the reference equation of Gibbons et al. (60) will be used to predict the normal 6MWD for each subject. Minimal normal 6MWD is defined as 82% of the predicted 6MWD (59). Information on the minimal clinically important difference (MCID) in 6MWD is important to assess the clinical relevance of the primary endpoint. These data are available from previous cited trials, including patients with foot drop due to central pathology (stroke, MS).

- The minimal clinically important difference was estimated at 50 meters in the study of Sankaranayan et al. (82).
- McLoughlin (83) estimated that a clinically meaningful increase in 6MWD by MS-patients is 100 meters (n=40). This number is based on the difference in 6MWD in patients with mild and moderate MS (defined using the Expanded Disability Status Scale (EDSS)) in Goldman's paper (86).
- Fulk (84) estimated the minimal important difference in 6MWD for stroke patients 2 months post-stroke. Fulk performed a secondary analysis of the data of the LEAPS rehabilitation trial (n=265)(87). Two anchors of important change were used: the modified Rankin Scale (mRS) and the Stroke Impact Scale (SIS). The estimated MCID of the 6MWD was 71 meters with the mRS as the anchor and 65 meters with the SIS as the anchor. For participants with initial gait speed (IGS) <0.40 m/s, the estimated MCID was 44 meters with the mRS as the anchor and 34 meters with the SIS as the anchor. For participants with IGS ≥0.40 m/s, the estimated MCID was 71 meters with the mRS as the anchor and 130 meters with the SIS as the anchor.
- In another publication, Fulk (85) determined the minimal detectable change (MDC_{90}) in rehabilitating stroke patients (n=37) defined as the amount of change that must be observed before the change can be considered to exceed the measurement error and variability at the 90% confidence level. For people who could walk without physical assistance, the MDC_{90} was 61 meters and for people requiring physical assistance, the MDC_{90} was 39 meters. Overall MDC_{90} was 54.1 meters.

The 6MWT is widely used to assess functional exercise capacity in cardiovascular and respiratory pathology (88). Bohannon (89) published a systematic review of reported MCID on the 6MWD in adults with pathology. They concluded that a change of 14.0 to 30.5 meters may be clinically important across multiple patient groups.

Based on the available data in the stroke and MS literature, the reference values in a normal population and the work of Bohannon, **we estimate the minimal clinically important difference in 6MWD in patients with foot drop due to peroneal nerve entrapment to be 10% of the minimal predicted age- and sex-specific reference value for that patient (see Appendix 5).** This value corresponds to a certain level with the range of MCID documented in stroke pathology. The MCID will be taken into account to determine relevance of the difference in 6MWD between the two patient groups. An example:

Suppose the baseline mean 6MWD is 300 meters in the conservative arm and surgical arm of the trial (no difference due to randomization). Mean difference in 6MWD in the surgical arm between baseline and 9 months is 120 meters and mean difference in 6MWD in the conservative arm between baseline and 9 months is 100 meters. Therefore, the difference between both groups is 20 meters. Apart from the assessment of statistical significance, the clinically relevant difference will be defined as the minimum of 10% of the mean minimal predicted age- and sex specific reference value of all patients in the conservative and surgical arm. E.g. assuming an average age of 55 years and 42% of the patients being female(3), the minimal mean predicted 6MWD would be 551.86 meters, resulting in a MCID of 55.2 meters. The actual value applied will be determined by the trial population.

Standardized 6MWT methodology is essential for reproducible and reliable results. The test should be performed in a minimally trafficked area along a flat, straight corridor ideally ≥ 30 meters in length (90, 91). Although the procedural guidelines, formulated in 2002, were made to address patients with respiratory pathology, several items can make the 6MWT in the foot drop trial more standardized:

1. Mark the starting line with brightly colored tape.
2. Mark the length of the hallway every 3m.
3. Mark turn around with a cone.

4. Patients should be wearing comfortable clothing and use their usual walking aids. The use of a foot-ankle orthosis is prohibited.
5. The patient should rest for at least 10 min prior to commencement of testing.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.
7. All patients will be instructed to cover as much distance as possible during six minutes.
8. Subjects will be encouraged every minute. The remaining time will be communicated every minute. An example: When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You have only 3 minute left.”
9. If the patient stops during testing, the timer should not be stopped. The time at which the patient stopped, and recommenced walking should be noted.
10. Walk distance is measured by counting the number of full laps and rounding to the nearest meter for the partial final lap.

The 6MWD will be evaluated twice at each visit (as first and last assessment), taking the ‘learning effect’ into account. Furthermore, the applied reference values are based on repeated 6MWD. Best 6MWD will be documented in the eCRF.

8.7.6 Ability to walk barefoot

Outcome based on patient interview/experience (yes / no). The ability to walk barefoot will be noted by the outcome assessor using the list of standard assessments at baseline, six weeks, 3 months, 6 months, 9 months and 18 months after randomization.

8.7.7 Stanmore Questionnaire

Through the Stanmore questionnaire, functional outcome can be assessed. The Stanmore questionnaire has been used in the literature to assess functional outcome in patients with foot drop due to peroneal nerve injury (94-96). Seven sections (pain, need for orthosis, normal shoes, functional outcome, muscle power, degree of active dorsiflexion and foot posture) add up to a sum score of 100 points. All cited studies used the same classification system for excellent, good, fair and poor:

- Excellent outcome: 85 to 100 points
- Good outcome: 70 to 84 points
- Fair outcome: 55 to 69 points
- Poor outcome: < 55 points

Gait assessment through the Stanmore Questionnaire is not considered standard of care. The Stanmore Questionnaire will be assessed by the outcome assessor at randomization, 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization.

Categories	Points
Pain (15 points)	
No pain at any time or not worse	15
Mild pain or slightly worse	10
Moderate pain or moderately worse	5
Severe pain or markedly worse	0
Need for orthosis (15 points)	
No	15
Occasional (once a week)	10
Frequently (twice a week)	5
Regularly (greater than twice a week)	0
Normal shoes (5 points)	
Yes	5
Yes, but prefers certain types	3
No	0
Functional outcome (10 points)	
Normal daily activity and normal recreation	10
Normal daily activity and limited recreation	6
Limited daily activity and recreation	3
Severe limitation on daily activity and recreation	0
Muscle power (modified Medical Research Council grading) (25 points)	
Grade 4+ or 5	25
Grade 4	20
Grade 3	10
Grade 2 or less	0
Degree of Active Dorsiflexion (degrees) (25 points)	
Greater than 6	25
0–5	20
−5 to −1	10
−10 to −6	5
less than −11	0
Foot posture (5 points)	
Plantigrade, balanced, no deformity	5
Plantigrade, mild deformity	3
Obvious deformity or malalignment	0
Total	100

The Stanmore questionnaire, as used in Yeap et al.(96)

8.7.8 Need for ankle-foot orthosis

The need for ankle-foot orthosis will be scored as part of the Stanmore questionnaire, but will be recorded separately as well (baseline, 6 weeks, 3 months, 6 months, 9 months and 18 months). The outcome assessor will document the need for an ankle-foot orthosis at each visit in the list of standard assessments and the eCRF.

8.7.9 Gait speed in the 10-meter walk test

Walking speed is an important aspect of gait and is often used as an objective measure of functional mobility. The 10-meter walk test is a commonly used and validated tool to assess gait speed.

To our knowledge, gait speed during the 10-meter walk test has not been mentioned in the assessment of foot drop due to peroneal nerve entrapment in the available literature. However, the test is used to assess gait speed in stroke literature (32, 82, 97) since gait velocity is a powerful indicator of function and prognosis after stroke (97) and the most efficient in predicting ambulation classification (98). In stroke literature, gait velocity is often interpreted in the context of community ambulation, broadly defined as locomotion outdoors to encompass activities such as visits to the supermarket, shopping mall and bank, social outings, vacations and pursuit of leisure activities (98, 99). Extrapolation of these data to patients with foot drop due to peroneal nerve entrapment needs to be done with caution, for the same reasons as mentioned in the discussing of the six-minute walk test. Lord (99) defined 4 ‘community ambulation groups’ in a sample of 130 post-stroke patients. Only patients discharged to a private home were included, which means that outcome after stroke was rather good. This improves the resemblance to patients with foot drop due to peroneal nerve entrapment.

- Community ambulation group 1 (not ambulant outside their home): 0.52 m/s (mean)
- Community ambulation group 2 (ambulant as far as the letterbox): 0.66 m/s (mean)
- Community ambulation group 3 (ambulant in the immediate environment): 0.82 m/s (mean)
- Community ambulation group 4 (ambulant in a shopping center and/or places of special interest): 1.14 m/s (mean)

Apart from the data from the stroke literature, reference values are available in the literature (100). Samson (101) defined reference values in a Dutch patient sample based on age and sex (see Appendix 6). Bohannon reported the MCID for change in comfortable gait speed measurements in patients with pathology in his systematic review (102). He concluded that changes in gait speed of 0.10 to 0.20 m/s may be important across multiple patient groups. Sankaranarayan estimated the MCID in gait speed in stroke patients to be 0.16 m/s (82).

Based on these data, **good outcome in terms of gait speed (m/s), as measured by the 10-meter walk test, is defined as gait speed ≥ 1.14 m/s. The MCID for gait speed in patients with foot drop due to peroneal nerve entrapment is estimated to be 0.15 m/s.**

In the 10-meter walk test, patients are instructed to walk at their usual, comfortable pace. Time is measured after a 5 meter stroke for acceleration (at the end there is a 5 meter stroke for deceleration (103). Determining gait speed through the 10-meter walk test is not considered standard of care. The 10-meter walk test will be carried out by the outcome assessor as baseline assessment, at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization.

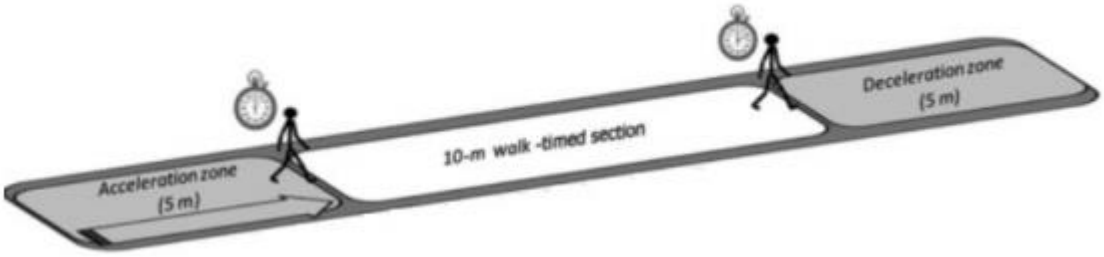


Figure 2. Set-up of the 10-meter walk test as described by Peters et al.(104).

Determining gait speed with the 10-meter walk test is not considered standard of care.

8.7.10 Sensory Changes

In a large retrospective patient series on peroneal nerve decompression after weight loss, Broekx et al. (2018) examined the recovery of sensory deficits (64). Symptoms qualified as sensory included the presence of hypoesthesia and/or paresthesia. They used the following system to assess sensory symptoms:

a. Complete recovery: the absence of any sensory symptoms
b. Partial recovery: patients with a minimum of sensory symptoms
c. No recovery: patients with no improvement

The same system will be used to assess and compare the evolution of sensory symptoms in the foot drop trial. Sensory changes will be evaluated at baseline and at the visits at 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization by the outcome assessor. Sensory changes at 10 days will be assessed by the treating physician. Documenting sensory function is considered standard of care.

8.7.11 Functional Ambulation Categories

Functional ambulation categories (FAC) (105) is a useful scale to assess gait in patients with foot drop. It is a six point scale, that is used in stroke literature (99, 106-109) and can help determine how much assistance a patient requires. A FAC ≥ 3 has been considered a surrogate of general walk ability in assessing mobility in stroke patients (108, 110). Mehrholz (111) showed a strong correlation between FAC and commonly used indicators of progress in gait performance. A FAC ≥ 4 could predict community ambulation with high sensitivity and specificity. Lord (99) assessed mobility in stroke patients. The highest

FAC was achieved by 72.3% of all 130 subjects and median FAC was 5. Again, extrapolation of these data is not ideal. However, taking all data into account, **good outcome correlates with a FAC of 5.**

Gait assessment through functional ambulation score is not considered standard of care. The FAC will be determined by the outcome assessor at baseline, 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization.

Functional ambulation categories (FAC)		
FAC 0	Nonfunctional	- No ambulation - Ambulation only in parallel bars - Requires supervision or physical assistance from > 1 person
FAC 1	Dependent (level II) MCID	- Requires manual contact of one person during ambulation on level surfaces - Manual contact is continuous and necessary to support body weight and/or to maintain balance and coordination
FAC 2	Dependent (level I)	- Requires manual contact of one person during ambulation on level surfaces - Manual contact is continuous or intermittent light touch to maintain balance/coordination
FAC 3	Dependent, supervision	- Ambulation occurs on level surfaces without manual contact of another person - Requires stand-by guarding of one person because of the need for verbal guidance or poor judgement or questionable cardiac status
FAC 4	Independent, level surfaces only	- Ambulation is independent on level surfaces - Requires supervision/physical assistance to walk stairs, inclinations or non-level surfaces
FAC 5	Independent, level and non-level surfaces	Ambulation is independent on non-level surfaces, inclinations and stairs.

8.7.12 Quality of life: the EQ5D-5L questionnaire

We will use the validated and commonly used EQ5D-5L (5 Level EUROQoL – 5 Dimensions) questionnaires to assess patient reported outcome measures (PROM). The EQ5D-5L questionnaires is attached to the protocol in Appendix 8. Assessing quality of life through the EQ5D-5L questionnaire is not considered standard of care. The questionnaire will be available as an online survey (REDCap) for the patients. If patients forget or don't want to use the online system, the outcome assessor will provide the questionnaire at the randomization visit, at 10 days (surgical group), 6 weeks, 3 months, 6 months, 9 months and 18 months after randomization and data will be collected in the eCRF. The treating physician

will provide the EQ5D-5L questionnaire at 10 days (surgical group) if a patient does not use the online system. This can only be done by the treating physician to guarantee blinding.

The EQ-5D 5L is a generic measure of health-related quality of life developed by the EuroQol Group. It is a validated measurement of quality of life widely used in different pathologies. The questionnaire is made up of two parts. The first part is descriptive and uses five different dimensions to score quality of life. These five dimensions are mobility, self-care, activities of the daily life, pain/discomfort and anxiety/depression. There are five different answer possibilities within each dimension, i.e. “no problem”, “slight problem”, “moderate problem”, “severe problem” and “unable to”. This renders 3125 different answer possibilities. The second part uses a visual analogue scale (VAS) to score the current health status of the patient, ranging from zero to one hundred. Zero corresponds to death and one hundred corresponds to a (subjective) perfect health status.

N.B.: Based on patient feedback throughout the pilot study, the SF-36 questionnaire will no longer be used. Patients experienced the questionnaire as too extensive. Furthermore, quality of life questionnaires were among the least popular trial assessments.

8.7.13 Surgical Complications

Overall, neurolysis of the peroneal nerve is considered a low-risk surgery (113)**.** Surgical complications will be assessed by the treating physician at 10 days and 6 weeks. This is considered standard of care. We will use a list of possible complications based on the available literature (1, 3, 43, 44, 47, 48, 50, 51, 55) and our own experience. In this way, surgical complications can be uniformly scored throughout all participating centers. Unforeseen complications will be recorded as free-text. After cross-over, surgical complications will be assessed by the outcome assessor at the extended follow-up visit (18 months).

List of predefined possible surgical complications:

Impaired/prolonged wound healing
Wound infection with need for antibiotics
Wound dehiscence without need for revision surgery
Wound dehiscence with need for revision surgery
Postoperative hematoma without need for revision surgery
Postoperative hematoma with need for revision surgery
(partial) Transection of peroneal nerve with new sensory deficit
(partial) Transection of peroneal nerve with new motor deficit
Persisting pain in the operated area
Development of complex regional pain syndrome

8.7.14 Treatment record

At every visit after the randomization visit (6 weeks, 3 months, 6 months, 9 months and 18 months), the outcome assessor should record several parameters of the ongoing physiotherapy program:

- Frequency of training
- Duration of training
- Home exercises
- Use of electrostimulation
- Total number of physiotherapy sessions
- Other therapies (vitamin substitution, acupuncture, …)

Other therapies are allowed, as long as they reflect daily practice. These therapies should be thoroughly noted in the eCRF. This registration is not considered standard of care.

8.7.15 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

Health economic aspects of foot drop will be evaluated through the Work Productivity and Activity Impairment Questionnaire (WPAI). The WPAI is widely used and validated in multiple languages. The WPAI allows for assessment of employment and professional productivity among other features. Participants will fill in the WPAI at baseline, 6 weeks and 6 months. WPAI will be available online. If the patient receives allowances, the amount will be noted for economic analysis. This is not considered standard of care. The English version of the WPAI is included in Appendix 7.

8.7.16 Return to work at six weeks after randomization

Health economic aspects will also be evaluated through the assessment of return to work. We expect subgroups of patients with foot drop to be unable to work. Once the foot drop has improved (or fully recovered), we expect patients to be able to return to work and to not experience any more related problems (after their initial recovery). In this trial population foot drop does in general not represent a chronic condition with periods of relapse. Either the foot drop recovers enough to be able to work again, or the foot drop does not sufficiently recover to resume previous professional activities.

Taking this into account, return to work seems to represent a very important measure. Patients will be asked about return to work at the study visit six weeks after randomization. To avoid recall bias, patients will be asked in advance to record the date of return to work. During baseline assessments, subjects will be questioned if they are incapacitated to work due to the foot drop and the last working day will be recorded in the eCRF.

We anticipate the biggest difference in return to work between the two groups at six weeks after randomization. We except patients to recover faster after neurolysis. Therefore, we expect that a significant majority in the surgically treated group will be able to return to work six weeks after randomization (equals five to six weeks after surgery), whereas recovery could be slower in the conservative group. Recovery from surgery itself is generally fast, thus we do not expect that surgical recovery has a big impact on return to work but of course this issue will also be tackled in the trial.

8.8 Table of trial procedures

TABLE OF TRIAL PROCEDURES	SCREENING	RANDOMIZATION[1]	TREATMENT PERIOD					EXTENDED FU PERIOD CROSS-OVER PATIENTS
		DAY 0	FU 10D (+4D) *surgery*	FU 6W (+ 1W)	FU 3M (+ 2W)	FU 6M (+ 2W)	FU 9M (+ 3W)	FU 18M (+ 3w)
INFORMED CONSENT	TP							
MEDICAL HISTORY	**TP**							
ELIGIBILITY CRITERIA	TP							
CONTRIBUTING FACTORS	**TP**							
EDX	**TP***				*		*	
ISOMETRIC DYNAMOMETRY		BR	TP	BR	BR	BR	BR	BR
6MWT		BR		BR	BR	BR	BR	BR
10MWT		BR		BR	BR	BR	BR	BR
RETURN TO WORK				**BR/P**				
FUNCTIONAL AMBULATION CATEGORIES		BR		BR	BR	BR	BR	BR
NEED FOR ORTHOSIS		**BR**		**BR**	**BR**	**BR**	**BR**	**BR**
ABILITY TO WALK BAREFOOT		**BR**		**BR**	**BR**	**BR**	**BR**	**BR**
STANMORE QUESTIONNAIRE		BR		BR	BR	BR	BR	BR
EQ5D-5L QUESTIONNAIRE		BR/P	TP/P	BR/P	BR/P	BR/P	BR/P	BR/P
SURGICAL COMPLICATIONS			**TP**	**TP**				**TP**
SENSORY CHANGES	**TP**	**TP/BR**	**TP**	**BR**	**BR**	**BR**	**BR**	**BR**
TREATMENT RECORD		**BR**		**BR**	**BR**	**BR**	**BR**	**BR**
WPAI		BR/P		BR/P		BR/P		
ADVERSE EVENTS		**TP**						
SERIOUS ADVERSE EVENTS		**TP**						
LEGEND	TP = treating physician; BR = blinded researcher (outcome assessor); bold = standard of care; P = patient (online survey); red = primary endpoint; FU = follow-up; D = days; W = weeks; M= months, YR = year *investigation performed by neurologist / rehabilitation physician, data collection in eCRF by study coordinator Some assessments are done by both the treating physician and blinded researcher to prevent bias/unblinding *! = surgery maximum one week after randomization, preferably within 2 days*							

8.9 Withdrawal criteria

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case, the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when the integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

The study design does not allow any cross-over to the other treatment arm until the primary endpoint is reached (9 months after randomization). Conservative care patients have the opportunity to undergo surgery after 9 months.

Subjects are considered withdrawn from the study if they:

- Are not willing to be followed up for the purposes of the trial at any further visits.
- State an intention to withdraw further participation in all components of the study.
- Are lost for follow-up (if all repeated attempts by the study-team to communicate with the individual have failed. The site and study team must take preventive measures to avoid a subject being lost to follow-up (at least 3 contacts (e.g., telephone calls, or e-mails) must be placed to the last available telephone number or e-mail address) and 1 registered letter must be sent by post to the last available home address. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.) In the source documents will be documented which steps have been taken to contact the participant.

Subjects are considered withdrawn from treatment if:

- The patient and/or patient's guardian does not wish to continue with further trial intervention.
- Choose for treatment in other arm (cross-over from conservative treatment to surgery).

A patient withdrawn from further treatment should remain in follow-up

Subjects are considered withdrawn from consent if:

- He/she withdraws consent to take part in the study without having to give a reason, and that may mean withdrawing his/her consent to the processing of health data.

If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward.

The details of withdrawal should be clearly documented in the patient's medical records and in the eCRF.

In the sample size of 182 subjects, there is an expected 5% dropout of patients (n=9). These subjects will not be replaced.

The sponsor reserves the right to terminate the study at any time globally or locally.

If a study is prematurely suspended or terminated, the sponsor will promptly inform the investigators and the Ethics Committee and provide the reasons for the suspension or termination. If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all enrolled subjects who are still in the study and/or their proxies/legal representatives (as applicable) and ensure appropriate treatment and follow-up.

8.9.1 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient's primary physician (GP) to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, every effort should be made so that follow-up information be obtained.

8.10 End of trial

The sponsor must notify the main EC of the end of a clinical trial within 90 days of its completion. End of trial is the date of the last visit/data item of the last patient in the trial.

9 TRIAL INTERVENTION

9.1 Surgical decompression of the peroneal nerve at the fibular head (neurolysis)

Surgical decompression of the peroneal nerve can be performed under local, locoregional or general anaesthesia. Pneumatic compression to restrict blood flow in the operation area during surgery can be used (and will be recorded in the surgery report).

The surgical approach for entrapment at the fibular head is usually through a curvilinear incision just distal to the fibular head. The length of the incision can vary between 3 and 10 centimeters. The subcutaneous tissue is bluntly dissected, and the common peroneal nerve is identified proximal to the peroneus longus muscle. The peroneal nerve is then released from the surrounding fibrous tissue and fascia. The anterior intermuscular septum is usually not cut, but this can be done if deemed necessary. The nerve is decompressed distally as it dives under the peroneus longus muscle. The decompression at this site is essential. Certain authors state that an adequate decompression should extend beyond the bifurcation in the deep and superficial peroneal nerve and should involve cutting the intermuscular septa (1, 114). It is up to the surgeon to decide if decompression beyond the bifurcation is necessary, based on intraoperative findings (recorded in the surgery report). Figure 3 illustrates the incision and decompression at the fibular head.

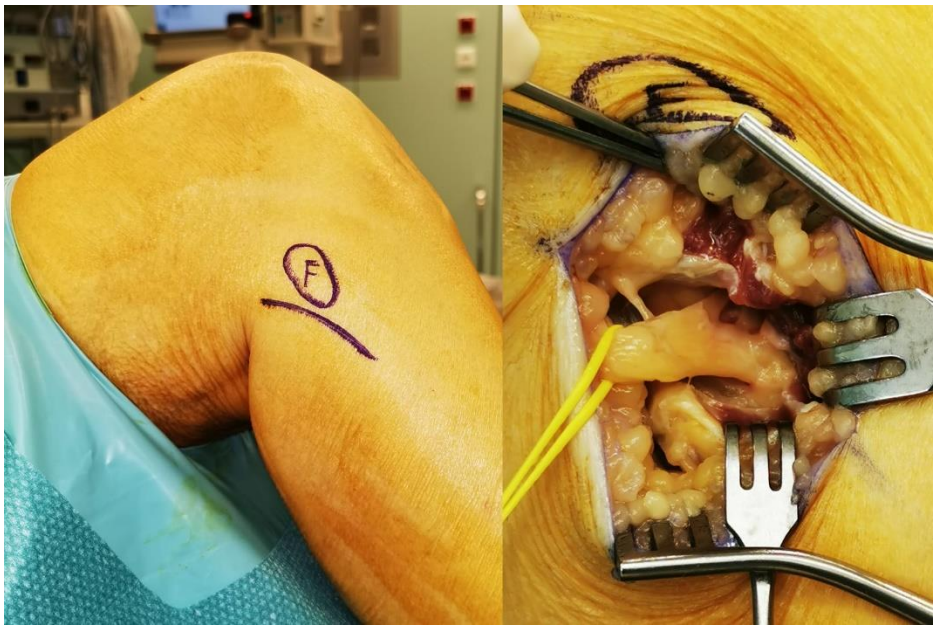


Figure 3. Surgical decompression of the peroneal nerve at the fibular head. *Courtesy of dr. F. Weyns*.

The patient will be hospitalized for up to 2 nights or can be operated on in an ambulatory day-care surgery setting. Postoperative treatment follows standard of care and can include physiotherapy and medication, a decision that is left to the treating physician.

A template for reporting the surgical procedure is made and included in appendix 9. All surgeons are advised to use this standardized template, since some technical aspects will be included in the eCRF (length of incision, cutting of the intermuscular septum, decompression beneath the fibular tunnel, decompression beyond the bifurcation, damage to the nerve).

9.2 Conservative treatment

Evidence on the conservative management of foot drop is scarce. Willerslev-Olsen et al. (115) found a significant improvement of foot and great toe dorsiflexion in children with cerebral palsy and foot drop after 1 month of gait training. Despite the lack of studies on training to improve foot drop of peripheral origin (as in peroneal neuropathy), a training program is recommended for every patient with foot drop (116). Goals of the treatment are to reduce muscle fiber atrophy, to preserve ankle mobility and to improve gait in general.

A basic standard protocol for physiotherapy is proposed. However, the protocol should be adapted to the clinical presentation and needs of every individual patient. So, if the trial should be mirroring daily practice, some degree of freedom in the conservative treatment should be allowed.

Standard instructions for the physiotherapist will be provided:

- Mobilization of ankle and foot, stretching of the calf muscles (prevention of contractures)
- Tonification of the dorsiflexion- and eversion muscles of the ankle
- Proprioceptive training
- Gait rehabilitation
- Home exercise schedule

Intensity: 60 sessions (F-pathology, Belgium) at a frequency of 1/2 sessions per week, with a possibility of a higher frequency during the first months.

The training program should be progressive. To evaluate the compliance, the patients will be asked to complete a training diary.

We do not advice to use electrostimulation because of the lack of training of younger physiotherapists and the lack of good equipment. The use of electrostimulation is not prohibited. We do not routinely support the use of an orthosis during the first six weeks. Most patients receive a prefabricated orthosis at this stage. However, this does not always meet the requirements of the patients at later stages. When the foot drop is irreversible, an ankle foot orthosis can help to improve everyday mobility.

10 SAFETY RECORDING AND REPORTING

10.1 Definitions

Term	Definition
Adverse Event (AE)	An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.
Adverse Reaction (AR)	An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

10.2 Recording of safety findings in function of the available evidence

The participant will be asked to report any adverse event related to the study-specific intervention to the study team. These reported events will be documented by the investigator in the source documents. The following minimum information should be recorded for each adverse reaction (AR) by the reporting investigator:

- AE description
- Start and stop date of the AR
- Severity
- Seriousness
- Causality assessment to the study interventions

- Outcome

The sponsor will keep detailed records of all AEs reported to him by the investigators and will perform an evaluation with respect to seriousness, causality and expectedness.

A Serious Adverse Event (SAE) is an untoward medical occurrence that results in any of the following:

- Death
- A life-threatening experience
- In patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect.

- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

When reporting adverse events to the sponsor, the investigator will protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the trial subject will be used in the report and the investigator retains the code to facilitate data verification by the sponsor and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events will be stated.
After the trial has been completed or terminated, all recorded adverse events will be listed, evaluated and discussed in the final report.

Reporting to the Ethics Committee
The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the EC.
The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC containing an overview of all SARs (Serious Adverse Reactions) occurred during the reporting period and taking into account all new available safety information received during the reporting period.

10.3 Data Safety Monitoring Board

Based on the European Medicines Agency (EMA) guidelines on data monitoring committees, the organisation of a Data Safety Monitoring Board is not necessary in the foot drop trial due to following reasons:

1. Peroneal nerve entrapment is no life-threatening disease.
2. The targeted patient population is to be expected to be able to signal any potential harm in an early stage in an appropriate manner.
3. There is no prior knowledge or strong suspicion that a treatment under consideration has the potential to harm patients.
4. The study design gives no reason for setting up a data safety monitoring board
5. The foot drop trial is a study in non-critical indications and both treatment modalities are well characterised, considered daily practice and known for not harming patients.

The independent experts in the TSC will act as an ‘extern advisory board’ to follow up on possible harm (e.g. related to late cross-over to surgery) and to follow up on blinding and accidental unblinding.

10.4 Notification of deaths

All deaths will be reported without delay to the EC (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event).

11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

Given that no reliable estimates of the 6MWD are available in this population, the sample size calculation is performed assuming a moderate effect size (mean difference divided by the standard deviation). Based on an effect size of 0.5, 172 patients would have 90% power to show a significant difference at a two-sided significant level of 5% in the change in the 6MWD from baseline to 9 months after randomization using a t-test. The sample size calculation was performed with G*Power, version 3.1.9.4. To compensate for an expected 5% dropout, a total of 182 patients (91 patients per group) will be included. The expected dropout rate of 5% is based on the results of patients interviews and a large, multicenter, randomised controlled trial comparing surgery versus non-surgery (or delayed surgery) with a design very similar to the foot drop trial (61, 62).

11.2 Sample size reassessment

A blinded sample size reassessment by the trial statistician is planned when 50% of the planned patients has reached their 9 month visit or one month before the final patient would be randomized, whichever occurs first. It will be based on the estimation of the overall variance of the primary outcome for the patients for which the primary endpoint data are available and the minimal clinical difference determined from all the patients randomized at that point. The maximum number of patients to be potentially added will be determined before the analysis will take place. It will among others be based on the recruitment rate. Full details of the analysis will be described in an interim analysis plan, which will be finalised after the pilot study and before the analysis will take place. Among others, it will contain the timing, the maximal number of potential extra number of patients to be recruited and the exact methods to be applied. Given that a blind analysis will be performed, the type I error will be preserved and no adjustment to the alpha level for the final analysis will be necessary. The trial will only potentially be extended but never terminated early based on this analysis.

11.3 Planned recruitment rate

A recruitment rate and recruitment strategy (table 3 and figure 4) was established for the full-scale study based on the following principles:

- A realistic inclusion rate for pilot study centers was established throughout the pilot study. This was taken into account to estimate a realistic recruitment potential for new centers.
- Based on additional retrospective data analysis in UZ Leuven and the recruitment rate in UZ Leuven during the pilot study, we do not expect any centre to randomize more than 10 patients per year
- All principal investigators were asked to estimate potential recruitment rate based on the number of patients treated in the past and their own experience.
- Centers will be initiated in two phases (see table 3). In a second phase, extra centers can be initiated if recruitment is going slower than expected. In a first phase we would like to start in centers that fulfil following criteria (based on the lessons learned during the pilot study):
    - Established multidisciplinary collaboration with all disciplines involved
    - Motivated study team
    - Centers from Brussels, Flanders and Wallonia
- The possibility of several new COVID-19 pandemic waves should be taken into account. This can slow patient recruitment and site initiating and therefore prolong patient inclusion
- Extra time should be taken into account since a sample size reassessment is planned during the course of the trial

Figure 4 visualises the recruitment strategy for the full-scale study. For every year of the full-scale study, we defined the (expected) maximal recruitment potential based on the estimated recruitment rate of the pilot study centers and phase 1 study centers. We also defined the number of patients that we minimally expect to randomize in the study. If this specific threshold is not reached, we can escalate by initiating the study in the phase 2 study centers. The start of the first year of the trial is defined as the date of the site initiating visit in the last participating phase 1 study centre (for simplicity it has been defined as the year 2023 in figure 5).

FOOTDROP PILOT STUDY CENTERS: **25 patients / year**

Centre	Principal investigator	Estimated recruitment rate / year
UZ Leuven	Prof. dr. Tom Theys	10 patients
ZOL Genk	Dr. Frank Weyns	5 patients
LUMC Leiden	Dr. Justus Groen	5 patients
AZ Groeninge Kortrijk	Dr. Jeroen Ceuppens	2 patients
CHU Liège	Prof. Dr. Annie Dubuisson	2 patients
ULB Erasme	Dr. Sophie Schuind	1 patient

FOOTDROP PHASE 1: **55 patients / year**

Centre	Principal investigator	Estimated recruitment rate / year
ZAS Antwerpen	Dr. Tony Van Havenbergh	5 patients
AZ Sint-Jan Brugge	Dr. Nikolaas Vantomme	5 patients
AZ Damiaan Oostende	Dr. Adinda De Pauw	5 patients
AZ Sint-Maarten Mechelen	Dr. Pieter Jan Van Dyck-Lippens	3 patients
AZ Turnhout	Dr. Jens Deckers	3 patients
AZ Alma	Dr. Kristel Vanchaze	3 patients
AZ Sint-Lucas	Dr. Kristel Vanchaze	3 patients
AZ Delta Roeselare	Dr. Jeroen Van Lerbeirghe	3 patients
AZ Vesalius Tongeren	Dr. Eveleen Buelens	3 patients
PHASE 1- CENTER 16	XXX	3-5 PATIENTS PER YEAR
PHASE 1 – CENTER 17	XXX	3-5 PATIENTS PER YEAR
PHASE 1 – CENTER 18	XXX	3-5 PATIENTS PER YEAR
PHASE 1 – CENTER 19	XXX	3-5 PATIENTS PER YEAR
PHASE 1 – CENTER 20	XXX	3-5 PATIENTS PER YEAR

FOOTDROP PHASE 2: **30 patients / year**

Centre	Principal investigator	Estimated recruitment rate / year
PHASE 2 – CENTER 1	XXX	3 -5 PATIENTS PER YEAR
PHASE 2 – CENTER 2	XXX	3-5 PATIENTS PER YEAR
PHASE 2 – CENTER 3	XXX	3-5 PATIENTS PER YEAR
PHASE 2 - CENTER 4	XXX	3-5 PATIENTS PER YEAR
PHASE 2 – CENTER 5	XXX	3-5 PATIENTS PER YEAR
PHASE 2 – CENTER 6	XXX	3-5 PATIENTS PER YEAR

Table 3 – FOOTDROP study centers

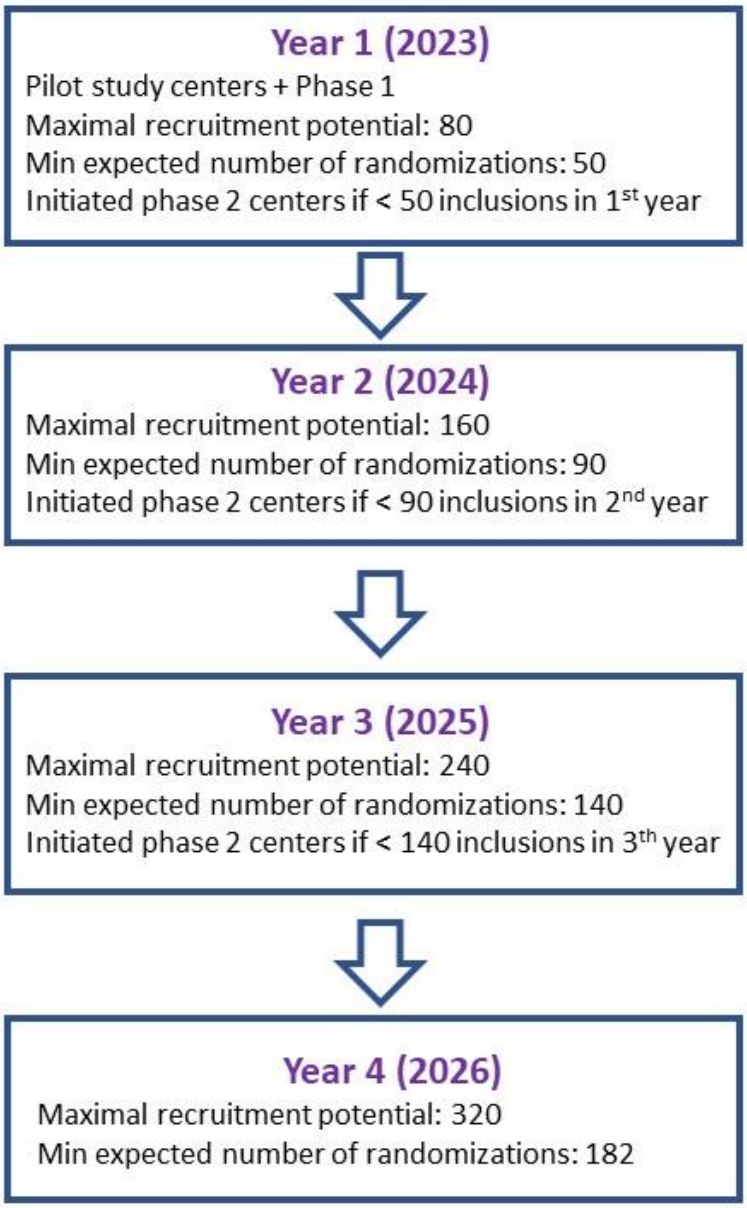


Figure 4 – Recruitment strategy

11.4 Statistical analysis plan

11.4.1 Analysis sets

The primary analysis will be the full analysis set (FAS) which will include all patients randomized. Patients will be analyzed in the group to which they were randomized, irrespectively which treatment was received, if any. In addition, a per protocol analysis set (PPS) will be used for sensitivity analyses. These will exclude patients or measurements from the FAS with major protocol violations like e.g., receiving surgery for patients randomized to the conservative arm within 9 months after randomization. All major protocol deviations that lead to exclusion from the PPS will be fully documented in the Analysis Sets Specification Document that will be dated and signed prior to database lock.

11.4.2 Summary of baseline data and flow of patients

Continuous variables will be summarized by treatment group by the number of non-missing data points, mean, standard deviation, median and interquartile range.

Categorical and ordinal variables will be summarized by treatment group by observed frequencies and percentages relative to the total number of non-missing items.

A CONSORT flow diagram (http://www.consort-statement.org/) will be produced to describe the flow of patients (65).

11.4.3 Primary outcome analysis

The distance covered during the six-minute walk test in meters (6MWD) at 9 months will be evaluated at each visit. A constrained longitudinal data analysis (cLDA) will be performed taking the correlation between these measurements into account. The value at baseline and all follow-up measurements will be taken as responses.

Indicators for baseline, follow-up visits, treatment group and the interaction between follow-up visits and treatment group will be included in the model. Missing data are appropriately taken into account with this model under the missing at random assumption. This is applicable to no-shows (patients that don't show up at study visits). For patients, refusing to participate in the 6MWT, zero as value will be recorded. We do not expect patients to not be able to perform the 6MWT due to peroneal nerve entrapment. All patients should be able to stand and walk a limited distance (if only the foot drop is taking into account). The primary analysis is the comparison between the two treatment groups of the difference in 6MWD between 9 months and baseline.

We will report the mean difference between the two treatment groups with a 95% confidence interval and a two-sided p-value. Superiority of surgery above conservative treatment will be claimed if $p < 0.05$ and the patients in the surgery arm improved more than the patients in the conservative arm.

Several sensitivity analyses will be performed. The first sensitivity analysis is similar to the primary analysis but with follow-up measurements after surgery not being used in the analysis for patients randomized to conservative treatment but who underwent surgery within 9 months. Similarly, follow-up measurements of patients randomized to surgery who did not undergo surgery will not be used in the analysis. This will allow to estimate the treatment effect most honestly. In the unlikely event that in the conservative treatment arm more than 10% cross-overs are observed, this sensitivity analysis will become the primary analysis and the primary analysis the first sensitivity analysis.

A second sensitivity analysis will be a multiple imputation analysis in which missing follow measurements will be imputed according to the conservative treatment arm for both the surgical and conservative treatment arm.

Full details will be made available in a statistical analysis plan (SAP), which will be finalized before database lock.

11.4.4 Secondary outcome analysis

The key secondary endpoint is the timing of recovery (defined as as the time necessary to cover the minimal age- and sex-specific normal distance in meters during the six-minute walk test AND the time necessary for foot drop to recover to a MRC-score ≥ 4 for ankle dorsiflexion). However, the study will be only powered for the primary endpoint but if the primary endpoint should show a significant difference, it is anticipated that also the timing of recovery might yield a significant effect. Motor strength will also be assessed at the following time points: at 6 weeks, 3 months, 6 months and 9 months. The time of recovery will be analysed using a generalized log-rank test with constant weights over time for interval-censored data. In addition, the Turnbull estimator with 95% confidence intervals will be produced. The estimated proportion of patients which are recovered will be estimated at 6 weeks, 3 months, 6 months and 9 months. We do not anticipate any mortality due to the pathology. In case a patient should die, the patient will be censored at his day of death.

Full details on the analysis of the key secondary endpoint and the analysis of the other secondary endpoints will be described in the SAP.

11.4.5 Procedure(s) to account for missing or spurious data

Real time data checks will be built into the data collection tool (eCRF) and further data management queries including missing data, out of range values, will be emailed to the centres on a regular basis, in accordance with the data management plan. Outstanding data queries will be reviewed on a regular basis by the trial coordinating and data management teams. Feedback will be provided to all centres on a regular basis.

Protocol deviations will be reviewed and classified (major/minor) on a regular basis by the trial co-ordinating team and will be escalated if recurring issues emerge. Major deviations will be flagged to the trial statistician and the trial Sponsor.

The handling of missing data will be described in the statistical analysis plan (SAP).

11.4.6 *Other statistical considerations.*

The analysis of the economic evaluation will be described in a separate analysis plan.

11.5 Data collection for economic evaluation

One of the goals of the KCE Trials programme is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind. The economic analysis itself is however not part of this protocol. Several characteristics of the foot drop trial make an economic analysis more feasible(117):

a. During the foot drop trial, there will be protocol-driven resource use that will bias costs in both treatment groups. There will be more hospital visits and technical investigations (EDX) than in standard of care. However, these extra costs are the same in both treatment arms and these costs are known. Bias will be very limited.

b. The comparator (prolonged conservative therapy) is relevant and considered daily practice.

c. We expect the recruiting centers to be representative of the larger population, given the large number of participating centers.

d. Compliance is not artificially enhanced.

e. The trial is designed to be naturalistic and to evaluate the effectiveness of interventions in real-life routine practice conditions.

Participation of Dutch centers can complicate economic analyses, since costs can differ substantially between different health care systems.

In a recent review Poage et al. (1) state that if a peroneal neuropathy is not treated properly the percentage of people with permanent motor weakness ranges from 30 to 35 %. The percentage of invalidity for a complete paralysis of the peroneal nerve is estimated at 22 % (European physical and mental disability rating scale for medical purposes (https://www.ecb.europa.eu/careers/pdf/annex_II_staff_rules_ft.pdf). De Bruijn (118) et al. reported on the economic impact of peroneal neuropathy in 19 patients. Nine of these patients (47%) with a paid job experienced some restrictions in work. Work adaptations were reported by two patients. No jobs were lost because of the nerve injury. In the OBSI (*officiële Belgische schaal ter bepaling van de graad van invaliditeit)*, the acknowledged percentage of invalidity due to severe limitations in ankle dorsiflexion (and/or plantar flexion) is 10 to 20% (http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2006020831&table_name=wet). During the pilot trial, the foot drop trial will assess the feasibility of documenting the percentage of invalidity, acknowledged by health care insurances.

Health-related Quality of Life data will be collected in both trial arms at baseline, 10 days, 6 weeks, 3 months, 6 months, 9 months and 18 months. Cost-effectiveness will be calculated as cost per quality-adjusted life-year (QALY) gained. Cost and utility impact will be derived from the analysis of individual patient data. Since peroneal neuropathy represents a common neuropathy and people with a permanent motor deficit will suffer from gait abnormalities (with the need for an orthosis and physiotherapy), as well as

chronic pain and possible skin problems due to sensory and autonomic deficits, we believe that this condition will have an important impact on quality of life. In addition to quality of life measures, the work productivity and impairment questionnaire (WPAI) will be used to assess employment and professional productivity. The WPAI will be collected at baseline, 6 weeks and 6 months. The professional occupation of patients will be collected as baseline data. Return to work will be assessed six weeks after randomization. We expect patients to be able to return to work after improvement (of recovery) of foot drop. Relapse of foot drop is not expected in the majority of cases (see also Section 8.7.16).

The proposed trial will provide the ideal opportunity to collect data about quality of life, surgical complications, employment and professional productivity in patients with a foot drop due to peroneal nerve entrapment. In addition, these data will provide further insights into the quality of life of people with a foot drop resulting from other aetiologies (such as lumbar disc herniation), and even about patients with other entrapment neuropathies.

The economic evaluation will be conducted from a healthcare payer (base case) and societal perspective. The aim of the economic evaluation is to measure, value and analyse total costs of patients in both groups and to relate the difference in costs between the two treatment groups to the difference in clinical effects. The time horizon of the economic evaluation is 18 months, after collection of all clinical data that can be used for the cost evaluation of the intervention. Sensitivity analysis will be performed to assess the robustness of the results using different assumptions regarding costs and effects.

Effect measures in the economic evaluation will be calculated by the available QOL-questionnaires (EQ-5D 5L at baseline, 6weeks, 3 months, 6 months, 9 months and 18 months). EQ-5D 5L is a sensitive QOL instrument in this trial, since mobility is one of the five dimensions of the EQ-5D 5L questionnaire. Therefore, we expect differences in outcome to be reflected in differences in EQ-5D 5L. EQ-5D 5L value sets are expected to be available at the end of the trial. If not, the EQ-5D-5L Crosswalk Index Value Calculator can be used. We expect to see a higher QOL for the surgical management of the foot drop.

To facilitate a later cost-utility analysis, quality of life data is collected during the trial (EQ-5D 5L). After the completion of the study the Sponsor will transfer the pseudonymised study data set to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g. IMA data by a trusted third party (TTP, eHealth platform) using the patient national number (see also 14.10 access to the study data by KCE and similar institutes in the EU).

This will allow to know the exact costs in both treatment arms, in which an important difference is to be expected. These costs are the costs of surgery, anaesthesia and hospitalisation in the surgical arm of the trial and costs of physiotherapy (F-pathology) in the conservative (and surgical) trial of the arm. The exact number of physiotherapy sessions will be recorded for all participants (treatment record). The costs of a foot-ankle orthosis will be documented as well (need for ankle-foot orthosis). If there is an unforeseen severe surgical complication, leading to hospitalization, these costs can be retrospectively determined through the national number of the patient. Other anticipated health care expenses are general practitioner care, costs of visits to other primary care providers, ambulatory and inpatient hospital care, medication and home care. The expected difference in these costs are expected to be relative minor and some of them are difficult to determine (home care), therefore, the economic analysis will not focus on these costs. Indirect costs include absenteeism from paid and unpaid work and presentism.

The incremental cost (ICER) will be calculated by dividing the difference in total costs between the treatment groups by the difference in mean effects (QOL) to compare both treatments.

12 DATA HANDLING

12.1 Data collection tools and source document identification

Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in Protocol and have provided written Informed Consent. Any and all side effects and adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the subjects concerning the study must also be recorded. The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided informed consent (i.e. to include randomized subjects and screening failures). This confidential subject identification provides the link between named subject source records in the subject file and pseudonymized eCRF data provided to sponsor. The Investigator must retain all study related documentation until at least 25 years after completion of the study. If regional regulations differ, the investigator must retain study related documents by whichever is longer. Study documents should not be destroyed without prior written agreement between the Investigator and sponsor. The sponsor must be notified if the Investigator wishes to assign the study records to another party or move them to another location.

Entries recorded by the subject on the paper copies of the Stanmore questionnaire and functional ambulation categories are considered source data (WPAI, SF-36, EQ-5D 5L and sensory changes will be filled in online through REDCap). Site personnel will review and ensure completeness of the subjects' entries.

Case report forms

A case report form (CRF) is a form on which individual patient data required by the trial protocol are recorded. REDCap will be utilized by trial site personnel to transfer trial data from source records (medical records and/or source document worksheets) onto common eCRFs (electronic Case Report Forms). This system is a web-based, secure electronic software application and will ensure that adequate collection of data has been performed:

- proper trails can be kept demonstrating the validity of the trial (both during and after the trial)
- only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)
- an annotated CRF is developed with coding convention as will be used in the database

12.2 Data handling and record keeping

All data relating to the Trial must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan will be developed to map data flows, data validation measures that will be taken and how (interim) database lock(s) will be managed.

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor.

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

12.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. The ISF and subjects' source documents must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

All essential documents will be archived for 25 years.

13 MONITORING, AUDIT & INSPECTION

Trial monitoring aims to verify that:

- the rights and well-being of human subjects are protected
- the reported trial data are accurate, complete and verifiable from source documents
- the conduct of the trial is in compliance with the currently approved protocol and amendment, with GCP and with the applicable regulatory requirements.

Prior to the start of the study, all required approvals must be obtained. During the study a monitor can contact and visit the site and must be permitted, on request, to access the study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the CRF. The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timelines of data collection. Monitoring can be done by exploring the trial dataset or by performing site visits.

The monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main endpoints. Additional checks of the consistency of the source data with the CRF will be performed according to the study-specific monitoring guidelines.

The requested subject files (ICF, medical notes, other documentation verifying the activities conducted for the study) should be available for review. The required study site personnel (see delegation log) must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study-related issues.

The investigator agrees to cooperate with the monitor to ensure that any issues detected in the course of these monitoring visits are resolved.

The frequency of visits will be specified in the trial monitoring plan.

The Investigator (and head of institution, if required by regional regulations) will make source data and documents for this study available to an appropriately qualified quality assurance auditor mandated by Sponsor or to regulatory authority inspectors, after appropriate notification.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Ethics Committee (EC) review & reports

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review and approval to Ethics Committee:

- before the start of the trial, approval will be sought from a EC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the FAMHP before they can be implemented in practice at sites)
- all correspondence with the EC will be retained in the Trial Master File/Investigator Site File
- an annual progress report (APR) will be submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- it is the Chief Investigator's responsibility to produce the annual reports as required.
- the Chief Investigator will notify the EC of the end of the study
- if the study is ended prematurely, the Chief Investigator will notify the EC, including the reasons for the premature termination
- within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the EC

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain an ICF for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR.

Data are **anonymous** if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.

When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately (site file) from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

14.2 Public and Patient Involvement

Patient involvement in the design of the research

Overall, 41 patients were involved in the trial design. All but one patient underwent treatment and were therefore biased. In total 32 patients were operated on and 9 patients were treated conservatively. One of the surgically treated patients underwent late neurolysis after extensive conservative treatment. Nevertheless, the reported information proved to be very useful. The information was collected in patient

interviews (almost exclusively by telephone given the COVID-19 pandemic). A single video-evaluation has been conducted. The purpose of patient involvement was to receive feedback on the design of the trial with the focus on choosing the primary and secondary endpoints relevant to patients. Furthermore, we wanted to assess willingness to participate in the trial. Treatment-related (e.g. would you undergo the same treatment again? Would you recommend this treatment to your family or a friend?), work-related (return to work) and health-related information (comorbidities) allowed for assessment of the impact of the disease and treatment on daily activities. Currently, no patient support groups and/or public initiatives exist for this pathology.

The following feedback from the patients was used in the design of the trial:

Choice of the primary outcome: a measure for gait analysis

In 93% of all patients, the success of treatment could be measured by improvement in gait. Improvement of gait could be measured as being able to walk long distances (either for professional or recreational purposes) or as a decreased risk of falling. Given the importance of gait impairment, the distance covered during the six-minute walk test was chosen as the primary outcome measurement. Several types of gait assessment were included as secondary endpoints.

Assessment of standard of care in peroneal nerve entrapment

Surgery was experienced as a safe procedure. Patient satisfaction was very high in the surgical group (93%), and complications rare (4%). Patient satisfaction in the conservative group was very high as well, with 90% of patients reporting to be satisfied with their treatment. All patients but one sought medical attention within six weeks after the onset of symptoms. 68% presented within the first week. A large proportion of patients followed intense physiotherapy. All patients, treated conservatively, followed at least 18 sessions. A high percentage of surgical treated patients followed physiotherapy, both pre- and postoperative. Ankle foot orthoses were not regularly used (in both treatment groups). Follow-up with EDX was more common in the conservative group (half of the patients underwent two electrodiagnostic evaluations) than in the surgical group (almost none had more than one EDX). Almost all patients were evaluated once after surgery. All patients were evaluated at least once during the conservative treatment. Half of these patients were evaluated at least two times.

Taking this information into account, the visits at three months, six months, 9 months and 18 months cannot be considered as standard of care. EDX after randomization cannot be considered standard of care.

Assessment of trial feasibility

71% of patients would be willing to participate in the proposed trial. The most frequent reason to refuse participation was related to the patient's profession. Many patients needed to be able to walk safely and often (for example a construction worker). They feared that, if they were not operated on, recovery would take longer, and they would not be able to return to work. Of course, these patients were biased, as most of them experienced fast and good recovery after surgery. The most frequent reasons to refuse participation in the conservative group were fear of the surgical procedure and the existence of significant comorbidities. However, even patients that would refuse to participate themselves, thought that other patients could certainly be interested as well. Taking into account that a biased patient sample was interviewed, 71% of inclusions represents a substantial number. In 97% of patients, a longer follow-up (with more investigations) would not be a reason to abstain from entering such trial.

During the pilot study we will have the opportunity to receive feedback from our subjects about the further trial.

Patients will be involved in the further set-up of the study, during the course of the trial and during the dissemination of the project results. We will also ask for feedback on the ICF. Patients will be involved in the development of the online tools for patients and will be asked to evaluate the different trial assessments for feasibility and relevance. (Online) patient meetings will be organised to collect feedback during the trial.

Patient feedback throughout the pilot study

Study assessments were evaluated by patients through a pilot study questionnaire, obtained at 6 weeks and 3 months after randomization. Opinions about different study assessments that are not considered standard of care are discussed below. Nine patients answered the pilot study questionnaire at 6 weeks and 3 months. Analysis is based on the data available from the start of the pilot study until the 7th of September 2022 (total of 18 questionnaires).

The six-minute walk test (6MWT)

Overall, the 6MWT was considered relevant, useful and completed without difficulties. At three months after randomization, two patients considered the 6MWT not useful (figure 5). From a patient perspective, the 6MWT seems to be a relevant and well chosen primary endpoint.

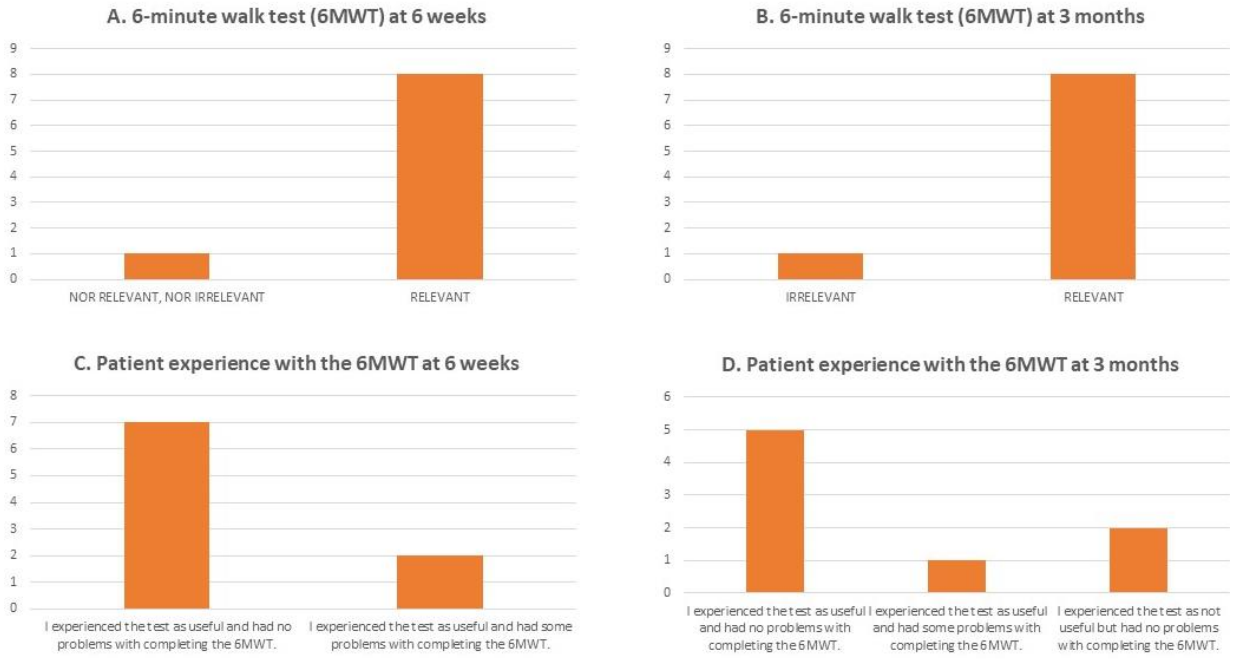


Figure 5 – The six-minute walk test during the pilot study

The 10 meter walk test (10MWT).

The 10-meter walk test was considered relevant by most patients. At 3 months, progressively more patients considered the 10MWT to be relevant compared to 6 weeks (figure 6).

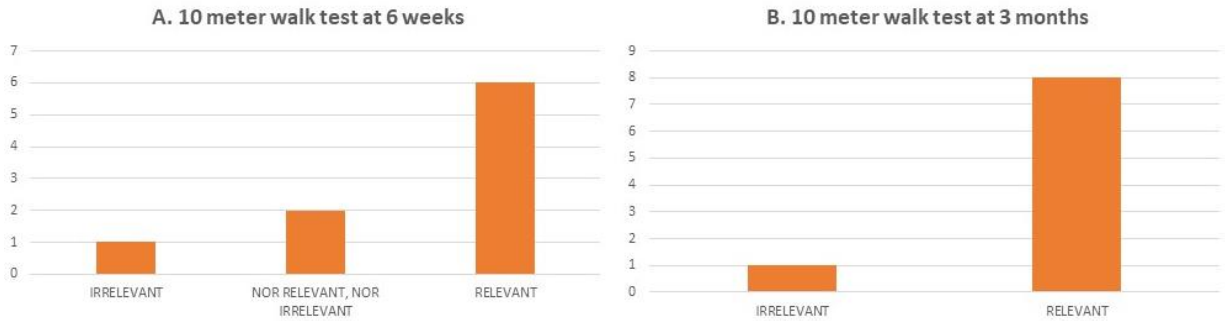


Figure 6 – The 10 meter walk test during the pilot study (figure 7)

Repeated electrodiagnostics

No patients considered EDX to be irrelevant. EDX is experienced as relevant by all patients at 3 months after randomization. (figure 7). We can conclude that patients find electrodiagnostics important in the follow-up of foot drop.

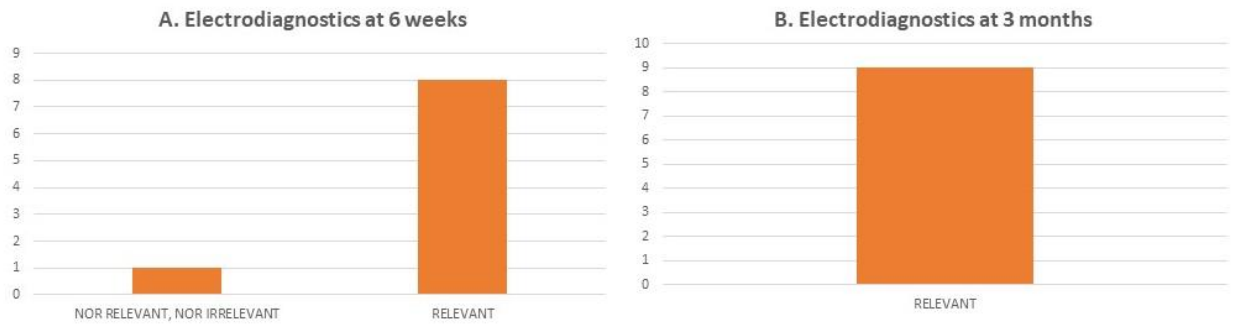


Figure 7 – Electrodiagnostics

Isometric dynamometry

An absolute majority of participants considered the assessment of motor function through isometric dynamometry to be relevant (see figure 8).

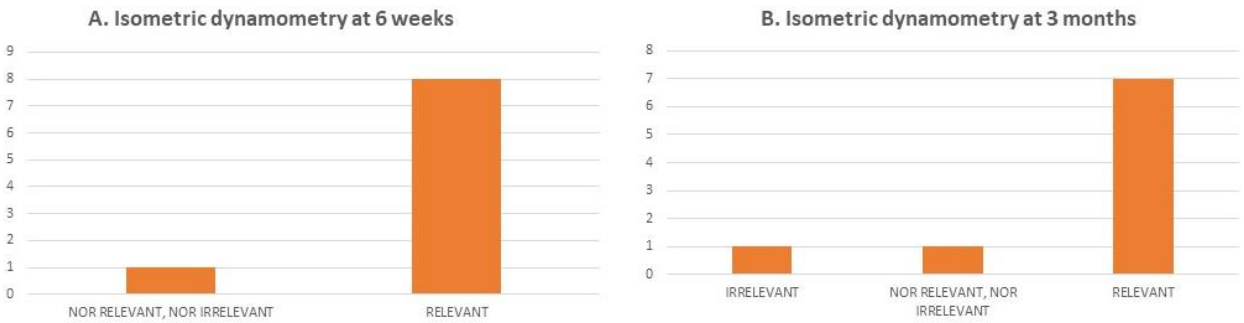


Figure 8 – Isometric dynamometry

Quality of life questionnaires (QoL)

Opinions regarding the quality of life questionnaires were more divided (figure 9). A little more than half of the participants considered the QoL questionnaires to be relevant at both evaluation moments. However, compared to the trial assessments discussed above, more patients considered QoL questionnaires to be less useful at both 6 weeks and 3 months. One patient in Leuven thought the SF-36 to be excessively long without any additional value over the EQ5D questionnaire.

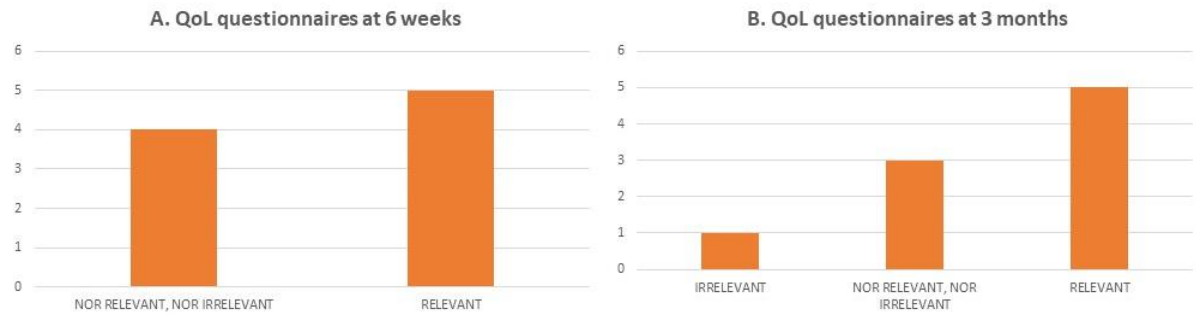


Figure 9 – Quality of life questionnaires

Work productivity and activity impairment questionnaire (WPAI)

Comparable to the quality of life questionnaires, opinions regarding the WPAI questionnaire were divided. However, the largest group of participants still considered the questionnaire to be relevant at both evaluation moments (figure 10).

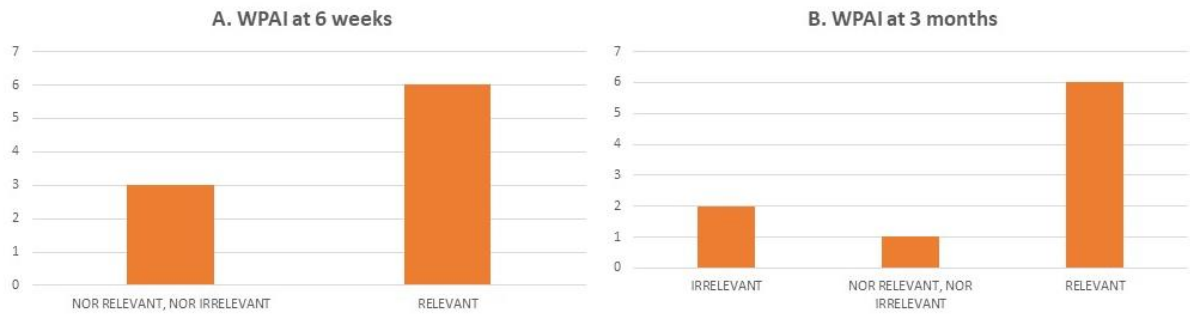


Figure 10 – Professional disability questionnaire

Other relevant pilot study questionnaire information

All patients understood the goal of the study and all patients acknowledged that they received enough information about the trial and the trial flow. All patients agreed that the instructions during the assessments were clear and understandable. The statements above were true both at 6 weeks and 3 months (1 questionnaire was incomplete regarding this topics). At 6 weeks after randomization, all patients (8), did not consider the study visits to be too time consuming. At 3 months, one patient thought the study visits were too time consuming. At 6 weeks, completion of the trial assessments took 71.25 minutes on average (minimum of 60 minutes, maximum of 90 minutes). At 3 months, completion of the trial assessments took 76.25 minutes on average (minimum of 30 minutes, maximum of 120 minutes).

Patients had the possibility to give other feedback in the questionnaire as well. A summary:

- "Due to the multiple appointments in a short period of time, the difference is really noticeable."
- "I am happy with the evolution of my foot."
- "It is important that there is a good connection between the patient and the physiotherapist. My physiotherapist gives me a good feeling!"
- "Surprised that there was no need for an operation, but all the better."
- "Since there is no progress, I do not think that it is useful to repeat the investigations this often. I am not making any staps forwards. I do not have pain, only hindrance. With pain I would not be able to complete all the assessments."

Apart from patient feedback from the questionnaire, we learned from one of our patients in UZ Leuven that perhaps too many questionnaires need to be completed repeatedly. Currently, patients need to complete 4 questionnaires: EQ5D-5L, SF-36, WPAI and the pilot study feedback questionnaire. This was discussed during the second Trial Steering Committee of 25-11-2021. The committee proposed to consider to exclude the SF-36 from the full-scale trial.After completion of the pilot study, the SF-36 questionnaire was omitted from the full-scale study.

14.3 Regulatory Compliance

The trial will not commence until a favourable opinion is obtained from the EC. The protocol and trial conduct will comply with applicable legislation, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

14.4 Protocol compliance

The investigator must conduct the study in compliance with the EC and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

Accidental protocol deviations can happen at any time. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the EC and regulatory authorities according to the sponsor or (overruling) local requirements.

All protocol deviations will be reported in the clinical study report. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

All participating physicians and trial sites have the responsibility to guide patients throughout the study visits and are expected to follow protocol and to inform patients in a correct, objective manner. If the TSC documents an unusual high percentage of cross-over in a specific trial site, this trial site can be excluded from the foot drop trial.

14.5 Notification of Serious Breaches to GCP and/or the protocol

It is understood that “a serious violation” is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

In that case, the Sponsor should be notified immediately upon becoming aware of a serious breach during the study conduct phase. The sponsor of a clinical will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial, or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

14.6 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Belgian and European Privacy legislation (http://www.dataprotectionauthority.be/legislation-and-standards) on the protection of privacy in relation to the processing of personal data, with regards to the collection, storage, processing and disclosure of personal information.

The investigator/delegate must ensure that data/patient confidentiality is maintained. On eCRFs or other documents (e.g., documents submitted to the EC or those attached to SAE forms) submitted to the sponsor, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator/delegate must keep a subject identification code list at the site, showing the subject number, the subject’s name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to the sponsor, and must be kept in strict confidence by the investigator/delegate.

14.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator and PIs at each site and committee members of the overall trial management have no competing interest.

14.8 Indemnity

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies.
Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law.

For non-Belgian Participating Sites

The Participating Site shall have and maintain in full force and effect during the term of this Trial (and for a reasonable period following termination of the Trial, adequate insurance coverage for other possible damages resulting from the Trial at the Participating Site, as required by local law. Each such insurance coverage shall be in amounts appropriate to the conduct of the services of the Participating Site under this Trial. The Participating Site and Sponsor shall be solely responsible for any deductible or self-insured retention under any such policies.

14.9 Access to the Study Data by KCE and similar institutes in the EU

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

A distinction is to be made by access by KCE (and similar institutes in Europe) and access by other parties.

Access to Study Data by KCE is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/en/resources-for-investigators

After the completion of the study the Sponsor will transfer the pseudonymised study data set to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g. IMA data by a trusted third party (TTP, eHealth platform) using the patient national number.

The patient information and consent includes wording that the national number will be recorded on site by the investigator for later data linkage, but will not be included in trial database available to the sponsor or any other third party. The patient information and consent will also include that in case the patient is randomized, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data. To this end, KCE will receive the link between the study number and the national number under pseudonymised form. KCE will never be able to use the link without authorisation of the ISC and the intervention of the TTP. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the patient that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by KCE. The processing of personal data for this analysis is necessary for the performance of a task carried out in the public interest, as specified in the law defining KCE's missions and tasks. To the extent the personal data is related to health, the processing is necessary for scientific or statistic purposes, as specified in the law defining KCE's missions and tasks. For all processing related to the analysis of effectiveness and cost-effectiveness of the intervention, KCE is the controller.

KCE and Sponsor have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.

"Background" means any intellectual property (IP), data, materials, information owned or controlled by the Sponsor or a Site, and required to run this Study. Sponsor will identify such Background including the legal restrictions of which Sponsor or Sites are aware that may affect the use of the Background for the purpose of the Study or the rights granted to KCE under this Agreement.

The Study Data consist of this protocol, including amendments, the electronic forms for data capture, including the annotations and guidance for use, the electronic database of the pseudonymized clinical and non-clinical data collected using data capture, including the log of changes from data entry to database

lock, study reports based on these pseudonymized data, and any data or reports generated at a later stage, e.g. based on exploratory analyses or stored samples.

“Foreground” means any Study Data, and any tangible biological, chemical and physical material and inventions, that are generated, acquired, discovered, conceived, developed, created, exemplified or derived as a result of carrying out the Clinical Study, whatever its form or nature, whether it can be protected or not, as well as any Foreground IP. Sponsor acknowledges that the main purpose of the research performed under this Agreement is to generate results that will serve the general public interests, and specifically the interests of the patients and public healthcare decision making bodies, and, therefore, undertakes not to exploit the Foreground in any way that is or could be detrimental to such interests.

The Sponsor owns the Study Data, but provides KCE with a copy of the pseudonymized database after database lock as well as a royalty-free unrestricted license to use the Study Data for non-commercial public health related purposes as detailed in the Agreement between KCE and <<Institution>> (details will be documented in the appropriate juridical documents). If judged appropriate, KCE will introduce the request to the competent chamber of the Information Security Committee and arrange for the data linkage. For the sake of clarity, the linked data are not part of the Study Data. However, KCE will discuss with the Sponsor the results of the analyses and the reporting of the linked data.

14.10 Access to the final trial dataset by other parties

The study results will be owned by the party who generates them. The Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE.

The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

15 DISSEMINATION POLICY

15.1 Dissemination policy

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

15.2 Authorship eligibility guidelines and any intended use of professional writers

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

For multicentre Trials, it is anticipated that the primary results of the overall Trial shall be published in a multicentre publication.

Participating Sites are not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

15.3 Communication plan

There is a consensus among experts that the results of clinical trials should be made available to participants and suggested that providing participants with results, both positive and negative, should be considered the "ethical norm"(119). This practice is being encouraged because it is a way of showing respect for research participants and to acknowledge the central role of participants in the completion of research studies. Communicating results avoids treating the participants as a means to an end (120). Although there are no strict guidelines formulated to share the results of trials with patients (121), the development of a communication plan is important. Therefore, a plan to communicate the results of the foot drop trial with all participants will be developed. Several barriers are taken into account:

1. Some patients might not want to know the results. Reactions to results may be influenced by an individual's coping style, how well he or she dealt with the foot drop. The response of the participant can also be affected by how the patient fared with the treatment. Patients may not want to know that they were allocated to the inferior arm of the trial. To address this concern, patients will be asked at the time of study enrollment if they wish to be offered trial results in the future. The informed consent form should both discuss potential benefits and risks of receiving results of the trial (122).
2. If the study participant has died or is not capable anymore of receiving the results himself or herself, psychosocial repercussions have to be anticipated when the family of the participant is contacted to discuss the results of the trial. Death or mental deterioration due to peroneal entrapment is not anticipated and highly unlikely.
3. The primary goal of clinical research is to seek generalizable knowledge. Physicians need to be aware that the results of the trial could not be beneficial for his/her own individual patient with whom he has a therapeutic relationship.
4. A fourth barrier is the absence of patient's groups. Therefore it is not possible to distribute trial specific information through patient group websites or patient communities, something that has been done in other trials (123).

Following guidelines to determine the appropriate time at which results would be offered to participants and to disseminate the plans are proposed. The proposed guidelines are partially based on the guidelines formulated by Fernandez et al. (124).

Willingness to receive trial related information.

Patients will be asked at the time of study enrollment if they wish to be offered trial results in the future. This will be included in the informed consent form. Both potential benefits and risks of receiving results of the trial will be discussed. If a patient chooses to not receive the trial results, this will be documented in the electronic case report form (eCRF). If a patient wants to receive the trial results, the patient can choose if he wants to be informed through e-mail or through a postal letter. If patients change their mind during the trial and choose to not receive the trial results, the study team can be addressed and the changes can be documented in the eCRF.

Trial results of full-scale trial

The results of the research will be communicated with the participants after all participants have reached the primary endpoint. This data will not be shared with participants until the data interpretation has undergone peer review. Research results should be offered in a timely manner and will therefore be

communicated within 1 month after the data are peer reviewed. Participants will receive an e-mail or postal letter that will address the following bullet points:

- The context and goals of the study will be documented, without the use of medical jargon.
- Major findings of the trial. The analyzed endpoints will be discussed.
- Limitations of the study.
- Any anticipated long-term effects
- Contact information of the site-specific clinical trial assistant will be provided to give participants the opportunity to ask for more / individualized information. This will also allow participants to receive additional information provided by the treating physician. This will allow to address medical or psychological needs of the research participants.
- The opportunity for patients will be provided to enlist to receive information on the extended follow-up period of 18 months. Only participants that want to receive additional information will receive this information. Results of the extended follow-up visit of 18 months will be communicated after the end of the trial, when all data have been analyzed and peer reviewed. These results will be made available within 3 months after this process.
- Gratitude towards the participants will be stressed in the communication.

Communication of results of the trial towards patients can be time consuming. Since the anticipated number of inclusions in the most centers is rather small, this should be feasible. The PI will be responsible for patient communication but can involve other staff or employees in a site-specific manner. In exceptional and unforeseen circumstances, bad information should always be discussed with the patient by the treating physician or PI.

16 REFERENCES

1. Poage C, Roth C, Scott B. Peroneal Nerve Palsy: Evaluation and Management. The Journal of the American Academy of Orthopaedic Surgeons. 2016;24(1):1-10.
2. Greenberg M. Peripheral nerves, entrapment neuropathies. Handbook of neurosurgery. 1. New York: Thieme; 2010. p. 515-40.
3. Broekx S, Weyns F. External neurolysis as a treatment for foot drop secondary to weight loss: a retrospective analysis of 200 cases. Acta neurochirurgica. 2018;160(9):1847-56.
4. Masakado Y, Kawakami M, Suzuki K, Abe L, Ota T, Kimura A. Clinical neurophysiology in the diagnosis of peroneal nerve palsy. Keio J Med. 2008;57(2):84-9.
5. Lezak B, Massel DH, Varacallo M. Peroneal (Fibular) Nerve Injury. StatPearls. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.; 2020.
6. Marciniak C. Fibular (peroneal) neuropathy: electrodiagnostic features and clinical correlates. Phys Med Rehabil Clin N Am. 2013;24(1):121-37.
7. Khedr EM, Fawi G, Allah Abbas MA, El-Fetoh NA, Zaki AF, Gamea A. Prevalence of Common Types of Compression Neuropathies in Qena Governorate/Egypt: A Population-Based Survey. Neuroepidemiology. 2016;46(4):253-60.

8. Kandil MR, Darwish ES, Khedr EM, Sabry MM, Abdulah MA. A community-based epidemiological study of peripheral neuropathies in Assiut, Egypt. Neurol Res. 2012;34(10):960-6.
9. Cruz-Martinez A, Arpa J, Palau F. Peroneal neuropathy after weight loss. J Peripher Nerv Syst. 2000;5(2):101-5.
10. Katirji B. Peroneal neuropathy. Neurol Clin. 1999;17(3):567-91, vii.
11. Poppler LH, Bansal A, Groves A, Sacks G, Davidge K, Mackinnon SE. Abstract 65: Subclinical Peroneal Nerve Entrapment May be an Under-recognized Cause of Falls in Hospitalized Patients. Plastic and reconstructive surgery. 2014;133(3 Suppl):76.
12. Poppler LH, Groves AP, Sacks G, Bansal A, Davidge KM, Sledge JA, et al. Subclinical Peroneal Neuropathy: A Common, Unrecognized, and Preventable Finding Associated With a Recent History of Falling in Hospitalized Patients. Ann Fam Med. 2016;14(6):526-33.
13. Poppler LH, Yu J, Mackinnon SE. Subclinical Peroneal Neuropathy Affects Ambulatory, Community-Dwelling Adults and Is Associated with Falling. Plastic and reconstructive surgery. 2020;145(4):769e-78e.
14. Weyns F, Bringmans T, Vandevenne J, Daenekindt T, Van Goethem A, Wuyts J, et al. Peripheral neuropathy caused by joint-related cysts: a review of 17 cases. Acta neurochirurgica. 2012;154(10):1741-53.
15. Tong O, Bieri P, Herskovitz S. Nerve entrapments related to muscle herniation. Muscle Nerve. 2019;60(4):428-33.
16. Elias WJ, Pouratian N, Oskouian RJ, Schirmer B, Burns T. Peroneal neuropathy following successful bariatric surgery. Case report and review of the literature. Journal of neurosurgery. 2006;105(4):631-5.
17. Sen O, Karaca FC, Turkcapar A. Neurological Complication After Laparoscopic Sleeve Gastrectomy: Foot Drop. Obes Surg. 2020;30(3):957-60.
18. Weyns FJ, Beckers F, Vanormelingen L, Vandersteen M, Niville E. Foot drop as a complication of weight loss after bariatric surgery: is it preventable? Obes Surg. 2007;17(9):1209-12.
19. Meylaerts L, Cardinaels E, Vandevenne J, Velghe B, Gelin G, Vanormelingen L, et al. Peroneal neuropathy after weight loss: a high-resolution ultrasonographic characterization of the common peroneal nerve. Skeletal Radiol. 2011;40(12):1557-62.
20. Lutte I, Rhys C, Hubert C, Brion F, Boland B, Peeters A, et al. Peroneal nerve palsy in anorexia nervosa. Acta Neurol Belg. 1997;97(4):251-4.
21. Katirji MB, Wilbourn AJ. Common peroneal mononeuropathy: a clinical and electrophysiologic study of 116 lesions. Neurology. 1988;38(11):1723-8.
22. Aprile I, Caliandro P, La Torre G, Tonali P, Foschini M, Mondelli M, et al. Multicenter study of peroneal mononeuropathy: clinical, neurophysiologic, and quality of life assessment. J Peripher Nerv Syst. 2005;10(3):259-68.
23. Bowley MP, Doughty CT. Entrapment Neuropathies of the Lower Extremity. Med Clin North Am. 2019;103(2):371-82.
24. Aprile I, Padua L, Padua R, D'Amico P, Meloni A, Caliandro P, et al. Peroneal mononeuropathy: predisposing factors, and clinical and neurophysiological relationships. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2000;21(6):367-71.
25. Pattyn R, Loder R, Mullis BH. Iatrogenic Peroneal Nerve Palsy Rates Secondary to Open Reduction Internal Fixation for Tibial Plateau Fractures Using an Intraoperative Distractor. J Orthop Trauma. 2020.
26. Farhad K, Traub R, Ruzhansky KM, Brannagan TH, 3rd. Causes of neuropathy in patients referred as "idiopathic neuropathy". Muscle Nerve. 2016;53(6):856-61.
27. Gloobe H, Chain D. Fibular fibrous arch. Anatomical considerations in fibular tunnel syndrome. Acta Anat (Basel). 1973;85(1):84-7.
28. Aprile I, Tonali P, Caliandro P, Pazzaglia C, Foschini M, Di Stasio E, et al. Italian multicentre study of peroneal mononeuropathy: multiperspective follow-up. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2009;30(1):37-44.
29. Eberstein A, Eberstein S. Electrical stimulation of denervated muscle: is it worthwhile? Med Sci Sports Exerc. 1996;28(12):1463-9.
30. Salmons S, Ashley Z, Sutherland H, Russold MF, Li F, Jarvis JC. Functional electrical stimulation of denervated muscles: basic issues. Artif Organs. 2005;29(3):199-202.
31. Terzis JK, Kostas I. Outcomes with microsurgery of common peroneal nerve lesions. J Plast Reconstr Aesthet Surg. 2020;73(1):72-80.
32. Bethoux F, Rogers HL, Nolan KJ, Abrams GM, Annaswamy TM, Brandstater M, et al. The effects of peroneal nerve functional electrical stimulation versus ankle-foot orthosis in patients with chronic stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2014;28(7):688-97.
33. Kluding PM, Dunning K, O'Dell MW, Wu SS, Ginosian J, Feld J, et al. Foot drop stimulation versus ankle foot orthosis after stroke: 30-week outcomes. Stroke. 2013;44(6):1660-9.

34. van der Linden ML, Andreopoulou G, Scopes J, Hooper JE, Mercer TH. Ankle Kinematics and Temporal Gait Characteristics over the Duration of a 6-Minute Walk Test in People with Multiple Sclerosis Who Experience Foot Drop. Rehabil Res Pract. 2018;2018:1260852.
35. Aprile I, Caliandro P, Foschini M, Di Stasio E, Padua L, Italian CTSaoESG, et al. Multicentre study of peroneal mononeuropathy: multiperspective follow-up of nonsurgical cases. J Peripher Nerv Syst. 12. United States2007. p. 232-3.
36. Smith T, Trojaborg W. Clinical and electrophysiological recovery from peroneal palsy. Acta neurologica Scandinavica. 1986;74(4):328-35.
37. Berry H, Richardson PM. Common peroneal nerve palsy: a clinical and electrophysiological review. Journal of neurology, neurosurgery, and psychiatry. 1976;39(12):1162-71.
38. Bsteh G, Wanschitz JV, Gruber H, Seppi K, Loscher WN. Prognosis and prognostic factors in non-traumatic acute-onset compressive mononeuropathies--radial and peroneal mononeuropathies. European journal of neurology. 2013;20(6):981-5.
39. Sipahioğlu S, Zehir S, Aşkar H, Işıkan UE. Peroneal nerve palsy secondary to prolonged squatting in seasonal farmworkers. Acta Orthop Traumatol Turc. 2015;49(1):45-50.
40. Sangwan SS, Marya KM, Kundu ZS, Yadav V, Devgan A, Siwach RC. Compressive peroneal neuropathy during harvesting season in Indian farmers. Trop Doct. 2004;34(4):244-6.
41. Fares MY, Dimassi Z, Fares J, Musharrafieh U. Peroneal neuropathy and bariatric surgery: untying the knot. Int J Neurosci. 2020;130(4):417-23.
42. Kim DH, Kline DG. Management and results of peroneal nerve lesions. Neurosurgery. 1996;39(2):312-9; discussion 9-20.
43. Fabre T, Piton C, Andre D, Lasseur E, Durandeau A. Peroneal nerve entrapment. The Journal of bone and joint surgery American volume. 1998;80(1):47-53.
44. Maalla R, Youssef M, Ben Lassoued N, Sebai MA, Essadam H. Peroneal nerve entrapment at the fibular head: outcomes of neurolysis. Orthopaedics & traumatology, surgery & research : OTSR. 2013;99(6):719-22.
45. Humphreys DB, Novak CB, Mackinnon SE. Patient outcome after common peroneal nerve decompression. J Neurosurg. 2007;107(2):314-8.
46. Kim DH, Murovic JA, Tiel RL, Kline DG. Management and outcomes in 318 operative common peroneal nerve lesions at the Louisiana State University Health Sciences Center. Neurosurgery. 2004;54(6):1421-8; discussion 8-9.
47. Mitra A, Stern JD, Perrotta VJ, Moyer RA. Peroneal nerve entrapment in athletes. Annals of plastic surgery. 1995;35(4):366-8.
48. Mont MA, Dellon AL, Chen F, Hungerford MW, Krackow KA, Hungerford DS. The operative treatment of peroneal nerve palsy. The Journal of bone and joint surgery American volume. 1996;78(6):863-9.
49. Morimoto D, Isu T, Kim K, Sugawara A, Yamazaki K, Chiba Y, et al. Microsurgical Decompression for Peroneal Nerve Entrapment Neuropathy. Neurologia medico-chirurgica. 2015;55(8):669-73.
50. Ramanan M, Chandran KN. Common peroneal nerve decompression. ANZ journal of surgery. 2011;81(10):707-12.
51. Sidey JD. Weak ankles. A study of common peroneal entrapment neuropathy. British medical journal. 1969;3(5671):623-6.
52. Solmaz I, Cetinalp EN, Gocmez C, Albayrak BS, Kural C, Kaya HS, et al. Management outcome of peroneal nerve injury at knee level: experience of a single military institution. Neurologia i neurochirurgia polska. 2011;45(5):461-6.
53. Souter J, Swong K, McCoyd M, Balasubramanian N, Nielsen M, Prabhu VC. Surgical Results of Common Peroneal Nerve Neuroplasty at Lateral Fibular Neck. World neurosurgery. 2018;112:e465-e72.
54. Horteur C, Forli A, Corcella D, Pailhe R, Lateur G, Saragaglia D. Short- and long-term results of common peroneal nerve injuries treated by neurolysis, direct suture or nerve graft. Eur J Orthop Surg Traumatol. 2019;29(4):893-8.
55. Tarabay B, Abdallah Y, Kobaiter-Maarrawi S, Yammine P, Maarrawi J. Outcome and Prognosis of Microsurgical Decompression in Idiopathic Severe Common Fibular Nerve Entrapment: Prospective Clinical Study. World neurosurgery. 2019;126:e281-e7.
56. Nirenberg MS. A simple test to assist with the diagnosis of common fibular nerve entrapment and predict outcomes of surgical decompression. Acta neurochirurgica. 2020;162(6):1439-44.
57. Lale A, Kirkil C, Ozturk S, Yur M, Can OF, Artaş G, et al. The results of surgical decompression in the treatment of foot drop due to peroneal nerve entrapment after bariatric surgery. Surg Obes Relat Dis. 2020.
58. Wilson C, Yaacoub AP, Bakare A, Bo N, Aasar A, Barbaro NM. Peroneal nerve decompression: institutional review and meta-analysis to identify prognostic associations with favorable and unfavorable surgical outcomes. Journal of neurosurgery Spine. 2019:1-8.

59. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. Eur Respir J. 1999;14(2):270-4.
60. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehabil. 2001;21(2):87-93.
61. Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, et al. Surgery versus prolonged conservative treatment for sciatica. The New England journal of medicine. 2007;356(22):2245-56.
62. Peul WC, van Houwelingen HC, van der Hout WB, Brand R, Eekhof JA, Tans JT, et al. Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial [ISRCT 26872154]. BMC musculoskeletal disorders. 2005;6:8.
63. Vaughan DW. Effects of advancing age on peripheral nerve regeneration. J Comp Neurol. 1992;323(2):219-37.
64. Broekx S WF. External neurolysis as a treatment for foot drop secondary to weight loss: a retrospective analysis of 200 cases. Acta neurochirurgica 160. 2018:(9):1847-56. doi:10.007/s00701-018-3614-9.
65. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.
66. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1384-7.
67. Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Respir J. 2011;37(1):150-6.
68. Camarri B, Eastwood PR, Cecins NM, Thompson PJ, Jenkins S. Six minute walk distance in healthy subjects aged 55-75 years. Respir Med. 2006;100(4):658-65.
69. Chetta A, Zanini A, Pisi G, Aiello M, Tzani P, Neri M, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. Respir Med. 2006;100(9):1573-8.
70. Shrestha SK, Srivastava B. Six Minute Walk Distance and Reference Equations in Normal Healthy Subjects of Nepal. Kathmandu Univ Med J (KUMJ). 2015;13(50):97-101.
71. Tsang RCC. Reference Values for 6-Minute Walk Test and Hand-Grip Strength in Healthy Hong Kong Chinese Adults. Hong Kong Physiotherapy Journal. 2005;23(1):6-12.
72. Marciniak C, Armon C, Wilson J, Miller R. Practice parameter: utility of electrodiagnostic techniques in evaluating patients with suspected peroneal neuropathy: an evidence-based review. Muscle Nerve. 2005;31(4):520-7.
73. Pugdahl K, Tankisi H, Fuglsang-Frederiksen A. Electrodiagnostic Testing of Entrapment Neuropathies: A Review of Existing Guidelines. J Clin Neurophysiol. 2020;37(4):299-305.
74. Derr JJ, Micklesen PJ, Robinson LR. Predicting recovery after fibular nerve injury: which electrodiagnostic features are most useful? Am J Phys Med Rehabil. 2009;88(7):547-53.
75. Aprile I CP, La Torre G, Tonali P, Foschini M, Mondelli M, Bertolliine C, Piazzini DB, Padua L. Multicenter study of peroneal mononeuropathy: clinical, neurophysiologic, and quality of life assessment. Journal of the Peripheral Nervous System 2005:10(3):259-68.
76. Visser LH, Hens V, Soethout M, De Deugd-Maria V, Pijnenburg J, Brekelmans GJ. Diagnostic value of high-resolution sonography in common fibular neuropathy at the fibular head. Muscle Nerve. 2013;48(2):171-8.
77. Compston A. Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain : a journal of neurology. 2010;133(10):2838-44.
78. Paternostro-Sluga T, Grim-Stieger M, Posch M, Schuhfried O, Vacariu G, Mittermaier C, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med. 2008;40(8):665-71.
79. Sardaru DP, Matei D, Zaharia-Kezdi D, Pendefunda L. Effects of biofeedback versus switch-triggered functional electrical stimulation on sciatica-related foot drop. J Back Musculoskelet Rehabil. 2018;31(2):239-45.
80. Steinau HU, Tofaute A, Huellmann K, Goertz O, Lehnhardt M, Kammler J, et al. Tendon transfers for drop foot correction: long-term results including quality of life assessment, and dynamometric and pedobarographic measurements. Archives of orthopaedic and trauma surgery. 2011;131(7):903-10.
81. Won YH, Kim KW, Choi JT, Ko MH, Park SH, Seo JH. Correlation between muscle electrophysiology and strength after fibular nerve injury. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2016;37(8):1293-8.
82. Sankaranarayan H, Gupta A, Khanna M, Taly AB, Thennarasu K. Role of ankle foot orthosis in improving locomotion and functional recovery in patients with stroke: A prospective rehabilitation study. J Neurosci Rural Pract. 2016;7(4):544-9.

83. McLoughlin J, Barr C, Sturnieks D, Lord S, Crotty M. Effect of wearing a dorsiflexion assist orthosis on mobility, perceived fatigue and exertion during the six-minute walk test in people with multiple sclerosis: a randomised cross-over protocol. BMC Neurol. 2012;12:27.
84. Fulk GD, He Y. Minimal Clinically Important Difference of the 6-Minute Walk Test in People With Stroke. J Neurol Phys Ther. 2018;42(4):235-40.
85. Fulk GD, Echternach JL, Nof L, O'Sullivan S. Clinometric properties of the six-minute walk test in individuals undergoing rehabilitation poststroke. Physiother Theory Pract. 2008;24(3):195-204.
86. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler. 2008;14(3):383-90.
87. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, et al. Protocol for the Locomotor Experience Applied Post-stroke (LEAPS) trial: a randomized controlled trial. BMC Neurol. 2007;7:39.
88. Nathan SD, du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015;109(7):914-22.
89. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. J Eval Clin Pract. 2017;23(2):377-81.
90. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. Chest. 2019.
91. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
92. Fong CM, Blackburn JT, Norcross MF, McGrath M, Padua DA. Ankle-dorsiflexion range of motion and landing biomechanics. J Athl Train. 2011;46(1):5-10.
93. Soucie JM, Wang C, Forsyth A, Funk S, Denny M, Roach KE, et al. Range of motion measurements: reference values and a database for comparison studies. Haemophilia. 2011;17(3):500-7.
94. Gatskiy AA, Tretyak IB, Tretiakova AI, Tsymbaliuk YV. Choosing the target wisely: partial tibial nerve transfer to extensor digitorum motor branches with simultaneous posterior tibial tendon transfer. Could this be a way to improve functional outcome and gait biomechanics? Journal of neurosurgery. 2019:1-9.
95. Reis FJ, Knackfuss I, Vercosa N, de Menezes SL, Gomes MK. A method used to access the functional outcome of tibial posterior tendon transfer for foot drop in leprosy. Foot Ankle Spec. 2012;5(1):45-50.
96. Yeap JS SD, Birch R. A method for evaluating the results of tendon transfers for foot drop. Clin Orthop Relat Res. 2001:(383):208-13. .
97. Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38(7):2096-100.
98. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke. 1995;26(6):982-9.
99. Lord SE, McPherson K, McNaughton HK, Rochester L, Weatherall M. Community ambulation after stroke: how important and obtainable is it and what measures appear predictive? Archives of physical medicine and rehabilitation. 2004;85(2):234-9.
100. Salbach NM, O'Brien KK, Brooks D, Irvin E, Martino R, Takhar P, et al. Reference values for standardized tests of walking speed and distance: a systematic review. Gait Posture. 2015;41(2):341-60.
101. Samson MM, Crowe A, de Vreede PL, Dessens JA, Duursma SA, Verhaar HJ. Differences in gait parameters at a preferred walking speed in healthy subjects due to age, height and body weight. Aging (Milano). 2001;13(1):16-21.
102. Bohannon RW, Glenney SS. Minimal clinically important difference for change in comfortable gait speed of adults with pathology: a systematic review. J Eval Clin Pract. 2014;20(4):295-300.
103. Peters DM FS, Krotish DE. Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults. . J Geriatr Phys Ther. 2013:36(1):24-30. .
104. Peters DM, Fritz SL, Krotish DE. Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults. J Geriatr Phys Ther. 2013;36(1):24-30.
105. Holden MK GK, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984:64(1):35-40. .
106. Lan Y XG, Huang DF, Mao YR, Chen SZ, Pei Z, et al. Association between improved trunk stability and walking capacity using ankle-foot orthosis in hemiparetic patients with stroke: evidence from three-dimensional gait analysis. . Chin Med J (Engl). 2013:126(20):3869-73. .
107. Wall A BJ, Vreede K, Palmcrantz S. A randomized controlled study incorporating an electromechanical gait machine, the Hybrid Assistive Limb, in gait training of patients with severe limitations in walking in the subacute phase after stroke. . PLoS One. 2020:15(2):e0229707. .

108. Timmermans C, Roerdink M, van Ooijen MW, Meskers CG, Janssen TW, Beek PJ. Walking adaptability therapy after stroke: study protocol for a randomized controlled trial. Trials. 2016;17(1):425.
109. Lan Y, Xu GQ, Huang DF, Mao YR, Chen SZ, Pei Z, et al. Association between improved trunk stability and walking capacity using ankle-foot orthosis in hemiparetic patients with stroke: evidence from three-dimensional gait analysis. Chinese medical journal. 2013;126(20):3869-73.
110. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984;64(1):35-40.
111. Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. Archives of physical medicine and rehabilitation. 2007;88(10):1314-9.
112. McHorney CA WJ, Lu JFR, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): III. Tests of Data Quality, Scaling Assumptions, and Reliability Across Diverse Patient Groups. . Medical Care 1994:32(1):40–66.
113. Ducic I, Felder JM, 3rd. Minimally invasive peripheral nerve surgery: peroneal nerve neurolysis. Microsurgery. 2012;32(1):26-30.
114. Anderson JC. Common Fibular Nerve Compression: Anatomy, Symptoms, Clinical Evaluation, and Surgical Decompression. Clin Podiatr Med Surg. 2016;33(2):283-91.
115. Willerslev-Olsen M, Petersen TH, Farmer SF, Nielsen JB. Gait training facilitates central drive to ankle dorsiflexors in children with cerebral palsy. Brain : a journal of neurology. 2015;138(Pt 3):589-603.
116. Carolus AE, Becker M, Cuny J, Smektala R, Schmieder K, Brenke C. The Interdisciplinary Management of Foot Drop. Dtsch Arztebl Int. 2019;116(20):347-54.
117. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(2):161-72.
118. de Bruijn IL, Geertzen JH, Dijkstra PU. Functional outcome after peroneal nerve injury. Int J Rehabil Res. 2007;30(4):333-7.
119. Partridge AH, Winer EP. Informing clinical trial participants about study results. Jama. 288. United States2002. p. 363-5.
120. MacNeil SD, Fernandez CV. Offering results to research participants. Bmj. 3322006. p. 188-9.
121. Macneil SD, Fernandez CV. Informing research participants of research results: analysis of Canadian university based research ethics board policies. J Med Ethics. 2006;32(1):49-54.
122. Donaldson S, Khetani N, Maniatis G, Stephens D, Wright JG. Sharing clinical trial results with adolescent idiopathic scoliosis patients. J Pediatr Orthop. 2009;29(5):467-75.
123. Dorsey ER, Beck CA, Adams M, Chadwick G, de Blieck EA, McCallum C, et al. Communicating clinical trial results to research participants. Arch Neurol. 2008;65(12):1590-5.
124. Fernandez CV, Kodish E, Weijer C. Informing study participants of research results: an ethical imperative. Irb. 2003;25(3):12-9.
125. Partridge AH, Wong JS, Knudsen K, Gelman R, Sampson E, Gadd M, et al. Offering participants results of a clinical trial: sharing results of a negative study. Lancet. 2005;365(9463):963-4.

■ APPENDICES

APPENDIX 1. RISK ASSESSMENT OF THE TRIAL INTERVENTION(S)

Risks associated with trial interventions ☒ **A ≡ Comparable to the risk of standard medical care** ☐ B ≡ Somewhat higher than the risk of standard medical care ☐ C ≡ Markedly higher than the risk of standard medical care
Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given): Both treatment arms are currently applied in daily clinical practice and application in this trial do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

APPENDIX 2. AUTHORISATION OF PARTICIPATING SITES

Appendix 2.1. Required documentation

- CV of the research team
- Certificate of good clinical practice (physicians)
- Confirmation of training of blinded researchers
- Confirmation of successful in training in REDCap data management

Appendix 2.2. Procedure for initiating/opening a new site

If the go criterion is met during the feasibility pilot study, the foot drop trial will be extended to a full-scale study. More than 20 centers in Belgium and several centers in the Netherlands will be included.

Appendix 2.3. Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the clinical study agreement.

A PI is expected to:

- Attend the initiation meeting/teleconference
- Supervise the training of the team members / blinded outcome assessors
- Ensure that the ISF is accurately maintained
- Report safety within the timelines
- Disseminate important safety or trial related information to all stakeholders within their sites

APPENDIX 3. AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	V.2.0	###	Christophe Oosterbos	Adaptation of protocol based on pilot study results. This amendment concers minor protocol adaptations: - Deletion of SF-36 as QOL questionnaire - Deletion of ankle dorsiflexion range of motion as study assessment The new recruitment strategy is included as well.

APPENDIX 4. LIST OF STANDARD ASSESSMENTS

MOTOR ASSESSMENT: MRC score for ankle dorsiflexion, ankle eversion and hallux-extension

Please use a score from 0 to 5 to grade the power of the muscle group in relation to the maximum expected for that muscle (compare to the contralateral healthy side).

Muscle group	MRC score (/5)
Ankle dorsiflexion	….
Ankle eversion	….
Hallux extension	….

SENSORY FUNCTION

Symptoms qualified as sensory included the presence of hypoesthesia and/or paresthesia. Please use following system to assess sensory symptoms (compare to the contralateral healthy side):

a. Complete recovery: the absence of any sensory symptoms
b. Partial recovery: patients with a minimum of sensory symptoms
c. No recovery: patients with no improvement

.....	.....	recovery

Ability to WALK BAREFOOT?

○ YES ○ NO

Need for FOOT-ANKLE ORTHOSIS?

○ YES ○ NO

TREATMENT RECORD

Physiotherapy: frequency	……. / week
Physiotherapy: duration per session	…… minutes
Additional Home exercises	Yes / No ……. / week (frequency)
Use of electrostimulation	Yes / No ……. / week (frequency)
Total number of physiotherapy sessions	…….. sessions
Other therapies (e.g. vitamin substitution, acupuncture, …)	……

APPENDIX 5. REFERENCE VALUES FOR 6-MINUTE WALK DISTANCE (6MWD) IN A NORMAL HEALTHY POPULATION

Appendix 5.1. Reference values for 6MWD in a healthy population aged 20 to 80 years

	Subject Age		
	20–40 years	*41–60 years*	*61–80 years*
Men			
N	19	12	10
Best 6MWD	800 ± 83 m	*671 ± 56 m	*687 ± 89 m
Women			
N	15	13	10
Best 6MWD	†699 ± 37 m	†670 ± 85 m	583 ± 53 m

SD: standard deviation; WD: walking distance.

Group means ± SD. Single factor ANOVA found a significant difference in best 6MWD across age groups in men ($F = 12.69$, $P < 0.0001$) and in women ($F = 11.2$, $P < 0.0002$). Post-hoc comparisons using Tukey's test revealed that best 6MWD was significantly greater in younger men than in middle-aged and older men. Post-hoc comparisons using Tukey's test revealed that best 6MWD was significantly lower in older women than in middle-aged and younger women.

*Significantly different from men aged 20 to 40 years.

†Significantly different from women aged 61 to 80 years.

JOURNAL OF CARDIOPULMONARY REHABILITATION AND PREVENTION

Variable	Coefficient	Cumulative r^2	Individual *P* value
Age (years)	2.99	0.25	<0.0001
Gender	74.7	0.41	<0.0001

WD: walking distance.

The model predicts best 6MWD as: 868.8 − (2.99*Age) − (74.7*gender) where men = 0 and women = 1. Although height was significantly related to best 6MWD in univariate regression analysis, it did not improve cumulative r^2 (individual *P* value < 0.97) when included in the model.

Table 3 * MULTIPLE LINEAR REGRESSION ANALYSIS OF BEST 6MWD

Reference values for the 6MWD per age-category as published by Gibbons et al. (60).

APPENDIX 6. AGE AND SEX-BASED REFERENCE VALUES FOR GAIT SPEED

Table 2 - *Mean and standard error of estimate (SE) of walking speed ($m \cdot s^{-1}$) presented by gender and decade of age.*

Decade of age	Women		Men	
Years	Speed	SE	Speed	SE
20	1.50	0.106	1.56	0.147
30	1.49	0.093	1.55	0.136
40	1.47	0.136	1.48	0.125
50	1.43	0.192	1.46	0.147
60	1.42	0.105	1.46	0.187
70	1.30	0.174	1.36	0.184
80	1.18	0.136	1.25	0.185

Mean estimate of walking speed (m/s) presented by gender and decade of age (101).

APPENDIX 7. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: GENERAL HEALTH

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

APPENDIX 8. QUALITY OF LIFE QUESTIONNAIRE

Appendix 8.1. EQ-5D 5L

The foot drop trial was registered at the EuroQol website with registration ID 39666. Included in Appendix 8 is the English version of the Health Questionnaires. The French and Dutch (for Belgium and the Netherlands) version are available as well.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

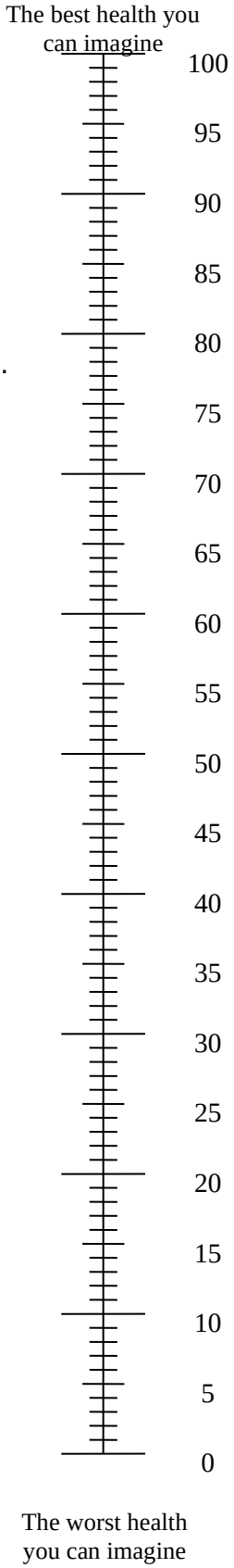
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 9. TEMPLATE FOR SURGICAL PROCEDURE

Surgical procedure: Neurolysis of the **right/left** peroneal nerve at the level of the fibular head

Anaesthesia: **Local / locoregional / general anaesthesia**

Surgical report:

Patient positioning: **supine/lateral with/without** pneumatic compression device.

Disinfection and sterile draping.

Curvilinear/linear incision of approximately ### centimetres beneath the fibular head.

The subcutaneous tissue is bluntly dissected, and the common peroneal nerve is identified proximal to the peroneus longus muscle. The peroneal nerve is then released from the surrounding fibrous tissue and fascia.

The anterior intermuscular septum **is/ is not cut**.

The peroneal nerve is decompressed distal to the fibular tunnel.

Decompression **does/does not** extend beyond the bifurcation in the superficial and deep peroneal branches.

The peroneal nerve **was/was not** damaged during the procedure.

Hemostasis.

Closure of the wound.

Estimated time of procedure (skin-to-skin: … mins).