Research Plan

Inspiratory muscle strength and respiratory complications after spinal cord injury: a multicenter, prospective cohort study

(HRO Annex 2/1.2; STROBE 1)

Type of Research Project:	State research type: research project in which health-related personal data is collected
Risk Categorisation:	Risk category A
Project Identifier:	RESCOM /2015-14
Project Leader:	Principal Investigator Dr. Gabi Müller Senior Scientist Clinical Trial Unit Guido A. Zäch Strasse 4 6207 Nottwil phone: +41 (0) 41 939 5563 e-mail: gabi.mueller@paraplegie.ch
Health condition / problem	Spinal Cord Injury / Respiratory muscle weakness
Project Duration	October 2016 - June 2019
Project Plan Version and Date:	Version 2, 27.7.2016

ACCESS TO RESEARCH DOCUMENTS

The access to research documents is not in conflict with applicable transparency rules.

SIGNATURE PAGE(S)
(swissethics 0, 1a)

Project number 2015-14
Project Title Inspiratory muscle strength and respiratory complications after spinal cord injury: a multicenter, prospective cohort study

The project leader and the methodologist have approved the research plan version 2, 27.7.2016 and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, the Principles of Good Clinical Practice (GCP) and the local legally applicable requirements.

Project Leader:

Dr. Gabi Müller

Nottwil 27.7.16
Place/Date / Signature

Project Methodologist

Dr. Martin Brinkhof

Nottwil, 27.07.2016
Place/Date / Signature

TABLE OF CONTENTS

SYNOPSIS (SUMMARY)

(HRO Annex 2/1.1)

Project Leader (or Sponsor)	Dr. Gabi Müller Senior Scientist Clinical Trial Unit Guido A. Zäch Strasse 4 6207 Nottwil, Switzerland phone: +41 (0) 41 939 55 63 e-mail: gabi.mueller@paraplegie.ch
Project Title:	Inspiratory muscle strength and respiratory complications after spinal cord injury: a multicenter, prospective cohort study
Short Title / Project ID:	RESCOM /2015-14
Project Plan Version and Date:	Version 2, 27.7.2016
Risk categorisation:	Risk category A
Type of Research:	Research project in which health-related personal data will be collected and used for further research. Only coded data will be used.
Project design:	Longitudinal, multi-centric cohort study (10 different centers worldwide)
Background and Rationale:	A spinal cord injury (SCI) often leads to paralysis of the respiratory m All data of drop-out patients will be anonymized after analysis. uscles, which causes a decrease in lung capacity and also in the ability to cough. Effective coughing is essential for airway clearance. With reduced cough capacity, the risk for pneumonia is increased. Pneumonia is still among the leading causes of death in the SCI population and one of the main complications after SCI. In a recent retrospective study of our lab we found first evidence that inspiratory muscle strength seems to be a very good discriminator between SCI individuals with and those without pneumonia. Nevertheless, these first results are based on retrospective data of one single center. Additionally, pneumonia is certainly influenced by many other parameters (personal-, lesion- and lifestyle characteristics) and has as well important impacts on e.g. quality of life and mortality. Nevertheless, these relationships are still assumptions which have to be proven in a large prospective cohort study.
Objective(s):	The main objective of this study is to evaluate 'cut-off levels' of inspiratory muscle strength as predictor for pneumonia in individuals with SCI (diagnostic accuracy). Additionally, to evaluate lifestyle and treatment parameters as well as personal- and lesion characteristics as further potential determinants of pneumonia as well as the impact of pneumonia on quality of life and mortality.
Endpoint(s):	<u>Primary study outcome:</u> Diagnostic accuracy of inspiratory muscle strength for prediction of pneumonia. <u>Main secondary study outcomes:</u> Personal- and lesion characteristics, other parameters of respiratory function, lifestyle and treatment parameters, quality of life and mortality due to pneumonia.

Inclusion / Exclusion criteria:	Inclusion: Male and female, age ≥ 18 years, AIS A, B, C or D lesion, lesion level C1-T12 Exclusion: Neurologic diseases (e.g. MS, ALS), 24h mechanical ventilation dependency, mental disorders
Project assessments, procedures:	Measurements: - in- and expiratory muscle strength (5min) - lung function (FVC, FEV_1, PEF, PCF) (10 min) Questionnaires: - ISCoS core data-set - ISCoS pulmonary function data sets - ISCoS quality of life questionnaire - questionnaire on individual respiratory muscle training, regular physical exercise and therapies - individual medication/vaccination and other medical complications will be assessed from patient's medical records All measurements will be performed at each measurement time-point (up to 4 times during inpatient rehabilitation) and last about 40 min per patient and measurement time-point in total (time with patient).
Number of Participants:	Regarding the in- and exclusion criteria, we made a calculation of a realistic numbers of subjects who can be recruited for this study per year and center, based on the number of patients admitted to the corresponding center during the last years.. Estimated numbers of patients per year for each center are as follows: Switzerland: SPZ Nottwil: 30 patients Balgrist Zuerich: 20 patients Rehab Basel: 20 patients CRR Sion: 5 patients Germany: BG Hamburg: 30 patients Austria: Haering: 30 patients Tobelbad: 30 patients Australia: Heidelberg: 40 patients The Netherlands: Rijndam: 20 patients Wijk aan Zee: 20 patients Overall, we will be able to recruit about 250 patients per year for this study. overall sample size: 625patients With an anticipated number of 625 subjects over a 2.5 years recruitment period, we may detect about 250 cases of pneumonia (under the assumption of a 40% incidence rate).
Project Duration, schedule:	The study is planned to start in October 2016 with the first patients included. The duration of the whole project will be 2.5 years of recruitment. Month Year of First-Participant-In (planned): October 2016 Month Year of Last-Participant-Out (planned): March 2019

Project Centre(s):	Multi-centric project Number of projected centers to be involved: 10 Number of projected countries to be involved: 5 <u>Switzerland:</u> • Swiss Paraplegic Centre Nottwil • University Hospital Balgrist, Zürich • REHAB Basel • Clinique romande de réadaptation Sion <u>Germany:</u> • BG Trauma Hospital Hamburg <u>Austria :</u> • Rehabilitationsklinik Tobelbad • Rehabilitationszentrum Häring <u>Australia:</u> • Austin Health, Melbourne <u>The Netherlands:</u> • Rijndam Rehabilitation Institute, Rotterdam • Heliomare Rehabilitation Center, Wijk aan Zee
Statistical Considerations:	To evaluate the diagnostic accuracy of markers of lung function (particularly MIP) for predicting or excluding clinical pneumonia we will use contemporary receiver operating characteristic (ROC) analyses techniques that allow for adjusting of covariate effects. Univariable and multivariable regression modelling will be used to evaluate the primary outcome and secondary outcomes. Multivariable modelling as compared univariable modelling will principally allow us to investigate relative contribution of different predictors (or risk factors) to the outcome of interest, while controlling for potential confounding by other factors. Multivariable models may further be used to examine effect modification (interaction) as well as mediation.
Other methodological Considerations:	Not applicable
Risk-Benefit statement:	Risk: ➢ Patients have to perform a maximum of 4 measurement sessions (dependent on the time of rehabilitation) with 40 min of measurements each. Therefore the time needed for this study will not negatively influence rehabilitation of included patients. Lung function and respiratory muscle strength measurements are non-invasive and also part of clinical routine. Safety of these measurements is very high and to the best of our knowledge we are not aware of any adverse events due to such measurements. Potential benefit of project result: ➢ Increased knowledge on determinants and effects of pneumonia will help to adapt rehabilitative strategies/therapy to prevent patients from pneumonia and thereby also increase quality of life of the patients and life expectancy.

ABBREVIATIONS

AIS	American Spinal Injury Association Impairment Scale
AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
CSC	Central Study Coordination
DoH	Declaration of Helsinki
eCRF	Electronic Case Report Form
CTU	Clinical Trial Unit
EC	Ethics Committee
FEV_1	Forced expiratory volume in 1 Second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HFG	Humanforschungsgesetz (Law on human research)
HRA	Federal Act on Research involving Human Beings
IMT	Inspiratory muscle trainer
ISCoS	International Spinal Cord Society
ISO	International Organisation for Standardisation
LSC	Local study coordinators LSC
LRH	Loi fédérale relative à la recherche sur l'être humain
LTI	Lower respiratory tract infections
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
PEF	Peak expiratory flow
PEP	Positive expiratory pressure
PI	Principal Investigator
ROC	Receiver operating characteristic
SCI	Spinal Cord Injury
SE	Serious event
STROBE	Strengthening the reporting of observational studies in epidemiology
QoL	Quality of life

SCHEDULE OF ASSESSMENTS (FLOW OF RESEARCH PROJECT)

(STROBE #5, 13c)

Time-Table RESCOM Study

	July 16	Aug 16	Sep 16	Oct 16	Nov 16	Dec 16	Jan 17	Feb 17	Mar 17	Apr 17	May 17	June 17	July 17	Aug 17	Sep 17	Oct 17	Nov 17	Dec 17	Jan 18	Feb 18	Mar 18	Apr 18	May 18	June 18	July 18	July 16	Aug 18	Sep 18	Oct 18	Nov 18	Dec 18	Jan 19	Feb 19	Mar 19	Apr 19	May 19	June 19
Study set-up (ethics approvals, local organisation of study sites, training of study nurses)																																				
Inpatient setting (2.5 years of patient recruitment)																																				
Analysis of inpatient setting																																				
Paper on inpatient setting																																				

Project Periods	Screening				
Visit	Before T1	T1	T2	T3	T4
Time-frame in days post injury (PI)		28±12	84±14	150±18	10 day before discharge until discharge
Screening: In- /Exclusion Criteria	x				
Participant Information and Informed Consent	x				
Demographics		x			
Medical History/medication/mortality		x	x	x	x
Co-morbidities (ICD-10)					x
Questionnaires: - ISCoS core data set, pulmonary function data set and quality of life data set - questionnaire on individual respiratory muscle training, regular physical exercise and therapies		x	x	x	x
Tests: - in- and expiratory muscle strength - lung function (FVC, FEV1, PEF, PCF)		x	x	x	x

1. ADMINISTRATIVE STRUCTURE

(HRO Art. 3, 4, Annex 2/1.8; swissethics 8a, 8b)

Sponsor, Project Leader and Coordinating researcher (if identical)	Sponsor: Swiss Paraplegic Centre Guido A. Zäch Str. 1 6207 Nottwil, Switzerland phone: +41 (0) 41 939 54 54 fax: +41 (0) 41 939 54 40 e-mail: spz@paraplegie.ch
Sponsor representative in Switzerland (if applicable), Project Leader (if different from Sponsor), Coordinating researcher in case of multicentre studies (if different from above)	Project Leader: Dr. Gabi Müller Guido A. Zäch Str. 4 6207 Nottwil, Switzerland phone: +41 (0) 41 939 55 63 fax: +41 (0) 41 939 64 65 e-mail: gabi.mueller@paraplegie.ch
Project site(s) and responsible researcher:	Dr. Gabi Müller Swiss Paraplegic Centre Nottwil Guido A. Zäch Strasse 4 6207 Nottwil, Switzerland e-mail: gabi.mueller@paraplegie.ch PD Dr. med. Martin Schubert University Hospital Balgrist Forchstr. 340 8008 Zürich, Switzerland e-mail: martin.schubert@balgrist.ch Dr. med. Margret Hund-Georgiadis REHAB Basel Im Burgfelderhof 40 4012 Basel, Switzerland e-mail: M.Hund@rehab.ch Dr. med. Xavier Jordan Clinique romande de réadaptation Av. Grand-Champsec 90 Case postale 352 1951 Sion, Switzerland e-mail: Xavier.Jordan@crr-suva.ch Prim.Univ.Prof.Dr. Renate Wildburger AUVA-Rehabilitationsklinik Tobelbad Dr.Georg Neubauer Str.6 8144 Tobelbad renate.wildburger@auva.at Prim. Dr. Burkhart Huber Rehabilitationszentrum Häring Rehaweg 1 6323 Bad-Häring, Austria

	Burkhart.Huber@auva.at
	Ass. Prof. David Berlowitz Austin Health 145 Studley Road PO Box 5555 Victoria Australia 3084 David.BERLOWITZ@austin.org.au
	Dr. Karin Postma Rijndam Rehabilitation Institute Westersingel 300 3015 Rotterdam, The Netherlands
	Prof. Dr. C.A.M. van Bennekom Heliomare R&D Relweg 51 1949 EC Wijk aan Zee Postbus 78, 1940 AB Beverwijk The Netherlands c.van.bennekom@heliomare.nl
	Dr. Sven Hirschfeld BG Trauma Hospital Hamburg Centre for Spinal Injuries Bergedorfer Str. 10 21033 Hamburg Germany S.Hirschfeld@buk-hamburg.de
Key Persons involved in research project:	Anja Raab, PhD student Swiss Paraplegic Centre Nottwil Guido A. Zäch Strasse 4 6207 Nottwil, Switzerland anja.raab@paraplegie.ch phone: +41 (0) 41 939 59 66
Other personnel	Data manager (SecuTrial®): Dr. Jörg Krebs Guido A. Zäch Str. 4 6207 Nottwil, Switzerland phone: +41 (0) 41 939 59 46 fax: +41 (0) 41 939 64 65 e-mail: joerg.krebs@paraplegie.ch
Project Methodologist/ biostatistician:	Dr. Martin Brinkhof Chief Scientific Officer SwiSCI Swiss Paraplegic Research Guido A. Zäch Str. 4 6207 Nottwil, Switzerland phone: +41 (0) 41 939 65 97 fax: +41 (0) 41 939 65 77 e-mail: martin.brinkhof@paraplegie.ch

2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study (HRA Art. 45-49; HRO, Art. 14, 17-23, Annex 2)

This research project will be carried out in accordance to the research plan and with principles enunciated in the current version of the Declaration of Helsinki (DoH), the Essentials of Good Epidemiological Practice issued by Public Health Schweiz (EGEP), the Swiss Law and Swiss regulatory authority's requirements as applicable. The EC and regulatory authorities will be informed about project start and termination.

2.2 Risk categorisation (HRO Art. 7, 33)

Our project corresponds to the Category A involving persons.
The measurement of respiratory muscle strength parameters represents no risk for the study participants. Apart from the determination of respiratory muscle strength, only one additional questionnaire will be performed during the course of this study (see 7.1 Project Flow Chart).

2.3 Ethics Committee (EC) and Competent Authorities (CA), FOPH (HRO Art. 14-23, 34, 37, 41, 45)

All project-specific documents will be submitted to a Ethics Committee before the project will be conducted.
The responsible investigator at each site ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the study.
No changes are made to the protocol without prior Ethic Committee and Sponsor approval, except where necessary to eliminate apparent immediate hazards to study participants. All changes in the research activity and all unanticipated problems will be reported to the CEC.
Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the EC within 90 days, the final study report shall be submitted within one year after study end.

2.4 Participant Information and Informed Consent (HRO Art. 8, Annex 2/1.3-1.5)

The investigators or study nurses of each participating site will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.
The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.
All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for the participant to make an informed decision about their participation in the study. Enough time (a minimum of 24hours) needs to be given to the participant to decide whether to participate or not.
The patient information sheet and the consent form will be submitted to the CEC and to the competent authority (as applicable) to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

See also Chapter 3.3 Risk-benefit assessment.

2.5 Participant privacy and safety (HRA Art. 1, Annex 2/1.7)

The Project Leader affirms and upholds the principle of the participants' right to dignity, privacy and health and that the project team shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual participant medical information obtained as a result of this research project is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to medical information in the computer files.
For data verification purposes, authorised representatives of the Sponsor, a competent authority (e.g. FOPH), or an ethics committee may require direct access to parts of the medical records relevant to the project, including participants' medical history.

2.6 Early termination of project (HRO Art. 22)

The sponsor, the project leader or the coordinating researcher may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

The premature end or interruption of the research project is reported to the EC within 90 days upon completion of the project.

2.7 Amendments, Changes (HRO Art. 18, 22, Annex 2)

Substantial amendments are only implemented after approval of the CEC.
All Non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. INTRODUCTION

(STROBE 2; HRO Annex 2/1.2)

3.1 Background

A spinal cord injury (SCI) often leads to paralysis of respiratory muscles (1), which causes a decrease in inspiratory volume and consequently limits the pre-cough volumes needed to produce an effective cough (2). The ability to cough is essential for airway clearance (3). With reduced cough capacity, the risk for pneumonia is increased (1). Pneumonia is still among the leading causes of death in the SCI population (4, 5). In acute SCI, up to 80% of patients are affected by respiratory complications (6) and in 51% of these cases pneumonia occurs (7), corresponding to a cumulative pneumonia incidence rate of about 40%. Unfortunately, predictors of pneumonia in SCI are still poorly understood (6).
To our knowledge, there are three studies on predictors of pneumonia in the SCI population (8, 9). Two of these studies concentrated on factors of injury and shock severity (9) or identified the level and completeness of injury as the fundamental clinical entity predicting pulmonary complications (8). However, both studies did not investigate potentially modifiable factors. The third study focused on potentially modifiable factors, such as lung function but did not cover respiratory muscle strength and did not define the inclusion of respiratory complications precisely (10). Therefore, to facilitate future evidence-based strategies to reduce the pneumonia risk in acute SCI, prevention targeted studies that aim to identify modifiable risk factors for pneumonia are urgently needed.
The current research proposal is targeted at specific parameters of respiratory function that are conceivably determinants of pneumonia risk as well as modifiable by respiratory muscle training (11, 12). In a recent study (accepted for Publication, Respiratory Care) we evaluated various respiratory function parameters and identified inspiratory muscle strength as a reliable discriminator between individuals with and those without pneumonia.
Although we identified inspiratory muscle strength as best parameter of respiratory function to discover individuals with SCI at risk for pneumonia, these data are based on a retrospective single-center data analysis without any detailed information on the type, time-point and severity of pneumonia. Also data on mortality due to pneumonia and other personal parameters that may influence the risk for pneumonia as well (e.g. smoking, exercise, mechanical ventilation dependency etc.) are missing in this analysis.

3.2 Rationale for the research project

To determine diagnostic accuracy of our concept of using 'cut-off levels' for inspiratory muscle strength to predict pneumonia in the management of SCI, replication in a large longitudinal multi-center cohort study is essential. Only a multi-center study may allow a larger sample size and the increase in power needed for an in-depth analysis of generalizability of and variation in 'cut-off levels' across settings and patient groups.

3.3 Risk-Benefit Assessment (HRA Art. 12; HRO Art. 15)

Patients have to perform a maximum of 4 measurement sessions (dependent on the time of rehabilitation) with 40 min of measurements each. Therefore the time needed for this study will not negatively influence rehabilitation of included patients. Lung function and respiratory muscle strength measurements are non-invasive and also part of clinical routine. Safety of these measurements is very high and to the best of our knowledge we are not aware of any adverse events due to such measurements.

Potential benefit of project result:
Increased knowledge on determinants and effects of pneumonia will help adapt rehabilitative strategies/therapy to prevent patients from pneumonia and thereby also increase quality of life of the patients and life expectancy.

4. OBJECTIVES, ENPOINTS/OUTCOMES AND OTHER STUDY VARIABLES

4.1 Objectives (STROBE 3)

The primary objective of the study is to evaluate diagnostic accuracy of 'cut-off levels' for inspiratory muscle strength as predictor for pneumonia in individuals with SCI.

Specific aims include:
1) to evaluate lifestyle and treatment parameters as well as personal- and lesion characteristics as potential other determinants for pneumonia;
2) to evaluate the association between pneumonia and quality of life as well as mortality due to pneumonia.

4.2 Primary and secondary endpoint/outcome(s) (STROBE #7)

Primary endpoint: Inspiratory muscle strength in relation to pneumonia

Secondary endpoints:
- mortality due to pneumonia
- quality of life
- other respiratory function parameters

Potential explanatory variables:
- personal and lesion characteristics (gender, age, height, weight, lesion level, AIS grade etc.)
- smoking status
- partly mechanical ventilation dependency
- medication and vaccination
- respiratory muscle training and physical exercise

4.3 Other study variables (STROBE #7)

not applicable

5. PROJECT DESIGN

(STROBE 4,5, 9; HRO Annex 2/1.2)

5.1 Type of research and general project design (STROBE 4)

Longitudinal, multi-centric cohort study (10 different centers, international)

5.2 Procedures (STROBE 5; swissethics 3a)

During inpatient rehabilitation 4 measurement time-points (T1-T4) will be used to assess longitudinal data of each participating patient.

Measurements:
- in- and expiratory muscle strength (5min)
- lung function (FVC, FEV_1, PEF, PCF) (10min)

Questionnaires:
- ISCoS core data-set (5min)
- ISCoS pulmonary function data sets (5min)
- ISCoS quality of life questionnaire (5min)
- questionnaire on individual respiratory muscle training, regular physical exercise and therapies (5-10min)

Individual medication/vaccination and other medical complications will be assessed from patient's medical records.

All measurements will be performed at each measurement time-point and last about 40 min per patient and measurement time-point in total (time with patient).
For the study nurse time needed per patient and measurement time-point (including planning, preparation, documentation and data entry) will be about 90 min.

5.3 Recruitment and Screening (swissethics 3b)

During a consecutive enrollment all patients, who fulfill the inclusion criteria, will be asked for participation by a skilled study nurse.

Screening tests:
- demographic data (age, language)
- severity and level of the lesion
- exclusion criteria

5.4 Methods of minimising bias (STROBE 9; swissethics 2)

Throughout the study, the coding of the participants will be conducted by the study nurses of each site in order to keep the data management and the biostatistician blind against the study condition as long as the data bank is open.

The coding list remains with the study nurses of each site for the whole duration of the study. Thus, coding will be conducted without any influence of the principal investigator or raters.
The study investigators will strive for complete separation of the individuals involved in the steps before enrolment from those involved in the data management and analysis.

Assessments of primary and secondary outcomes will be conducted by a study nurse without any influence on data analysis. All study nurses will go through a profound assessment training program.
A study nurse will enter data into the secuTrial® data management system so that the biostatistician can analyze the data without having access to information about the origin, or names of participants.

6. PROJECT POPULATION

(STROBE 6; HRO Annex 2/1.2)

6.1 Inclusion criteria

Initial rehabilitation after SCI, men and women, age ≥ 18 years, AIS A, B, C or D lesion, lesion level C1-T12

6.2 Exclusion criteria

Neurologic diseases (e.g. MS, ALS), 24h mechanical ventilation dependency, mental disorders

6.3 Criteria for withdrawal / discontinuation of participants

Reasons for which a participant needs to discontinue from the project:

- withdrawal of informed consent
- non-compliance
- medical complications which do not allow measurements of this study
- death

In case of drop-out, the already recorded data will be used for further analyses. All data of drop-out patients will be anonymized after analysis.

We will report all reasons for withdrawal of the participants and compare the reasons qualitatively.

The study will not be stopped in case of futility, unless CTU Nottwil during the course of safety monitoring advices otherwise. In this case, CTU Nottwil will discuss potential stopping for futility with the study investigators group.
The final decision to terminate the study is taken by the Principal Investigator of the study.

7. PROJECT ASSESSMENTS

(STROBE 7; HRO Annex 2/1.2)

7.1 Project flow chart(s) / table of procedures and assessments

Project Periods	Screening				
Visit	Before T1	T1	T2	T3	T4
Time-frame in days post injury (PI)		28±12	84±14	150±18	10 day before discharge until discharge
Screening: In- /Exclusion Criteria	x				
Participant Information and Informed Consent	x				
Demographics		x			
Medical History/medication/mortality		x	x	x	x
Co-morbidities (ICD-10)					x
Questionnaires: - ISCoS core data set, pulmonary function data set and quality of life data set - questionnaire on individual respiratory muscle training, regular physical exercise and therapies		x	x	x	x
Tests: - in- and expiratory muscle strength - lung function (FVC, FEV1, PEF, PCF)		x	x	x	x

7.2 Assessments of primary endpoint/outcome

The primary endpoint of this study is the diagnostic accuracy of inspiratory muscle strength for predicting or excluding clinical pneumonia. Diagnostic accuracy of positive and negative results will be evaluated by the area under the receiver operating characteristic (ROC) curve, which provides an operational measure of the intrinsic ability of the diagnostic test by offsetting the true positive rate against the false positive rate (13). Based on our previous evidence, MIP was defined as the primary diagnostic lung parameter (14). The potential additive diagnostic value of various other lung parameters, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), peak cough flow (PCF) and maximum expiratory muscle strength (MEP) will also be investigated. The two measures for the primary endpoint, maximal inspiratory pressure (MIP) and the event of clinical pneumonia, are assessed as follows.

Inspiratory muscle strength will be measured using a hand-held respiratory pressure meter (Micro RPM, Micro Medical, Hoechberg, Germany) by an independent study nurse of each participating study site. All measurements will be performed with the patients sitting upright in their own wheelchair. Patients have to breathe through a mouthpiece while wearing a nose clip. Each measurement will be repeated three times. The greatest value of each parameter will be used for analysis (15).

For each event of pneumonia the following information will be recorded: date of event; duration of event; physician diagnosed; and type. The differentiation of the type of pneumonia is important and will be evaluated using patients medical records data following the pneumonia flow diagram of "Disease and Control Prevention / National Healthcare Safety surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting" (16). To determine the type of pneumonia the methods x-ray, signs and symptoms and the laboratory are used. Finally four different types of pneumonia can be diagnosed.

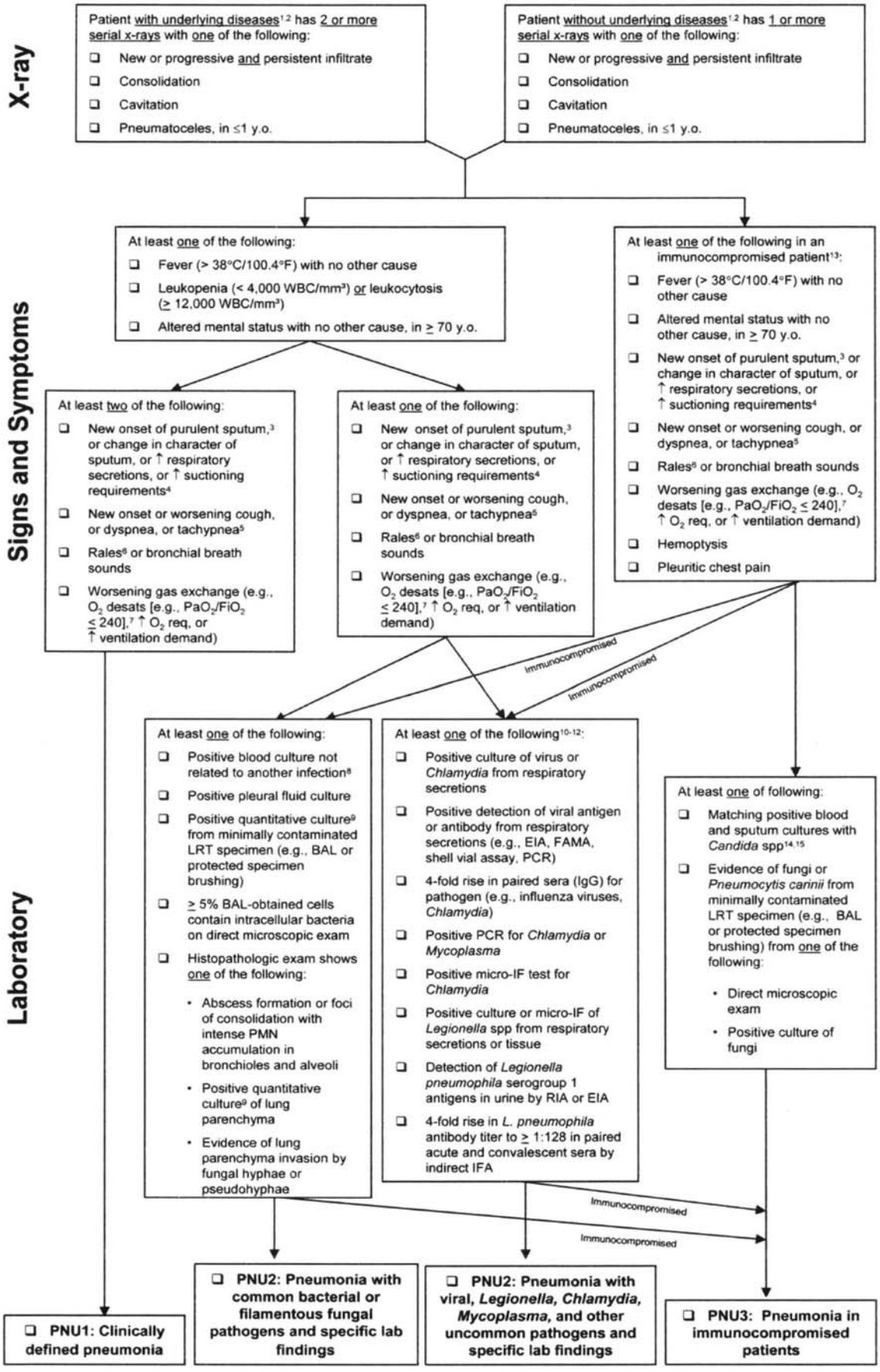
Pneumonia 1: clinically defined pneumonia

Pneumonia 2: pneumonia with common bacterial or filamentous fungal pathogens and specific lab findings

Pneumonia 3: pneumonia with viral and other uncommon pathogens and specific lab findings

Pneumonia 4: pneumonia in immunocompromised patients

Figure 1: Pneumonia flow diagram for patients of any age (16).


X-ray
Patient with underlying diseases[1,2] has 2 or more serial x-rays with one of the following:
❑ New or progressive and persistent infiltrate
❑ Consolidation
❑ Cavitation
❑ Pneumatoceles, in ≤1 y.o.
Patient without underlying diseases[1,2] has 1 or more serial x-rays with one of the following:
❑ New or progressive and persistent infiltrate
❑ Consolidation
❑ Cavitation
❑ Pneumatoceles, in ≤1 y.o.
Signs and Symptoms
At least one of the following:
❑ Fever (> 38°C/100.4°F) with no other cause
❑ Leukopenia (< 4,000 WBC/mm³) or leukocytosis (≥ 12,000 WBC/mm³)
❑ Altered mental status with no other cause, in ≥ 70 y.o.
At least one of the following in an immunocompromised patient[13]:
❑ Fever (> 38°C/100.4°F) with no other cause
❑ Altered mental status with no other cause, in ≥ 70 y.o.
❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
❑ Hemoptysis
❑ Pleuritic chest pain
At least two of the following:
❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
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❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
Immunocompromised
Immunocompromised
Laboratory
At least one of the following:
❑ Positive blood culture not related to another infection[8]
❑ Positive pleural fluid culture
❑ Positive quantitative culture[9] from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing)
❑ ≥ 5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam
❑ Histopathologic exam shows one of the following:
• Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli
• Positive quantitative culture[9] of lung parenchyma
• Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae
At least one of the following[10-12]:
❑ Positive culture of virus or *Chlamydia* from respiratory secretions
❑ Positive detection of viral antigen or antibody from respiratory secretions (e.g., EIA, FAMA, shell vial assay, PCR)
❑ 4-fold rise in paired sera (IgG) for pathogen (e.g., influenza viruses, *Chlamydia*)
❑ Positive PCR for *Chlamydia* or *Mycoplasma*
❑ Positive micro-IF test for *Chlamydia*
❑ Positive culture or micro-IF of *Legionella* spp from respiratory secretions or tissue
❑ Detection of *Legionella pneumophila* serogroup 1 antigens in urine by RIA or EIA
❑ 4-fold rise in *L. pneumophila* antibody titer to ≥ 1:128 in paired acute and convalescent sera by indirect IFA
At least one of following:
❑ Matching positive blood and sputum cultures with *Candida* spp[14,15]
❑ Evidence of fungi or *Pneumocytis carinii* from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing) from one of the following:
• Direct microscopic exam
• Positive culture of fungi
Immunocompromised
Immunocompromised
❑ PNU1: Clinically defined pneumonia
❑ PNU2: Pneumonia with common bacterial or filamentous fungal pathogens and specific lab findings
❑ PNU2: Pneumonia with viral, *Legionella, Chlamydia, Mycoplasma*, and other uncommon pathogens and specific lab findings
❑ PNU3: Pneumonia in immunocompromised patients

7.3 Assessment of secondary endpoint/outcome(s)

Secondary endpoints of this study include the various lung parameters mentioned above; other medical complications; quality of life; co-morbidities, medication and vaccination and mortality, in particular pneumonia-related death.

The various lung parameters thus include maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP), vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak expiratory flow (PEF).

The peak cough flow (PCF) will be measured by having the person cough as forcefully as possible through a peak flow meter.

Medical complications will be assessed from the patient's medical records by the study nurse without involvement of the patient.

Quality of life (QoL) will be evaluated using the Quality of Life Basic Data Set of the International Spinal Cord Injury Datasets. This measurement instrument accepts (QoL) as a multi-facetted concept and includes three questions as to capture general quality of life (overall well-being), rating of physical health, and satisfaction with psychological health (17).

Co-morbidities will be assessed only once using the ICD-10 codes after the end of inpatient rehabilitation. This will also be assessed from the patient's medical records by the study nurse without involvement of the patient.

Medication and vaccination will be assessed at each measurement time-point (T1-T4) from the patient's medical records by the study nurse without involvement of the patient.

Mortality will be defined as pneumonia-related, if a prevailing event of pneumonia was clinically resolved as the initiating factor of the cascade of morbid events leading directly to death. Similarly, other causes of death will be recorded as part of all-cause mortality and as potentially competing risks of death.

7.4 Assessment of safety and reporting (HRO Art. 20. 21)

An annual safety report will be submitted once a year to the local Ethics Committee via local Investigator.
For multi-center studies the annual safety report contains information from all sites including information from sites outside of Switzerland. The Sponsor-Investigator prepares it, and then submits it to the participating Investigators. The participating Investigators submit it to the local committees.

7.4.1 Definition of Serious Events (SEs) (HRO Art. 21)

A **serious event** is any unfavourable event for which a causal relationship to sampling of biological material or the collection of health related personal data cannot be ruled out, and which:

- requires hospitalisation or prolongation of an inpatients' hospitalisation,
- results in persistent or significant disability or incapacity, or
- is life-threatening or results in death,

If a serious event occurs the research project will be set on hold.

7.4.2 Assessment and Documentation of SEs
(HRO Art. 20, 21)

The assessment will be done by the Principal Investigator with regard to the project-specific measure relation according to the following definitions:
Unrelated: The occurrence of the event has no temporal relationship to the project-specific measures applied and can be explained by the underlying disease or other factors.
Related: There is a plausible temporal relationship between the occurrence of the event and the project-specific, applied measures and cannot be explained by the underlying disease or other factors.

All SEs will be documented in the participants´ file and on the SE report form. A sample form is appended to the Protocol and can be downloaded at www.swissethics.com.

7.4.3 Reporting of SEs, Safety and Protective Measures
(HRO Art. 20)

The Principal Investigator will report any occurring SE to the responsible EC within 7 days (and to the FOPH in case of involved radioactive sources). She will also submit a report which evaluates the relationship between the event reported and the methods of collecting health related personal data or sampling of biological material within that project, furthermore proposals how to proceed with the project.
The Principal Investigator will notify the EC within 7 days of any immediate other safety and protective measures, which have to be taken during the conduct of the research project. In addition, the Principal Investigator will explain the circumstances, which necessitated the safety and protective measures.

All SAEs will be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.
SAEs resulting in death will be reported to the local Ethics Committee (via local Investigator) within 7 days.
The other in the trial involved Ethics Committees will receive SAEs resulting in death in Switzerland via Sponsor-Investigator within 7 days.

8. STATISTICAL METHODOLOGY

8.1 Determination of Sample Size
(STROBE 10)

Regarding the in- and exclusion criteria, we made a calculation of a realistic numbers of subjects who can be recruited for this study per year and center, based on the number of patients admitted to the corresponding center during the last years.
Estimated numbers of patients per year for each center are as follows:

Switzerland:	SPZ Nottwil:	30 patients
	Balgrist Zürich:	20 patients
	Rehab Basel:	20 patients
	CRR Sion:	5 patients
Germany:	BG Hamburg:	30 patients
Austria:	Haering:	30 patients
	Tobelbad:	30 patients
Australia:	Heidelberg:	45 patients
The Netherlands:	Rijndam:	20 patients

Heliomare: 20 patients

Overall, we will be able to recruit about 250 patients per year for this study.
Overall sample size: 625 patients
With an anticipated number of 625 subjects over a 2.5 years recruitment period, we may detect about 250 cases of pneumonia (under the assumption of a 40% incidence rate (6, 7).
Moreover, taking the diagnostic accuracy (i.e., area under the curve (AUC)) of 0.86 from a retrospective study as reference (14), the envisioned sample size of at least 250 cases per diagnostic group should allow for detecting a diagnostically and clinically relevant effect (i.e., change in AUC) of 0.07 to 0.05 with 95% confidence level and 80% power (18).

8.2 Data processing

To ensure the consistency of data collection across clinics, relevant definitions, terminology used and descriptions of procedures will be described in a data manual (RESCOM Dataset Handbook) available to all local study coordinators (LSC). The LSC will be supervised by the Central Study Coordination (CSC) to guarantee adherence to standard operation procedures. The LSC will enable real time monitoring of enrolment of participants to CSC to early identify difficulties. Data storage, validation, monitoring, update, backup and analysis will be performed centrally at the CSC following established procedures. The CSC is hosted by Clinical Trial Unit of the Swiss Paraplegic Centre in Nottwil.

All study data from RESCOM are encrypted. Personal data of participants will be stored in the local clinic database. Both study data and personal data will contain a unique identifier (RESCOM ID number) allowing to link the datasets when needed. For all data analyses, only the encrypted research data set (study data) will be used. Personal data will only be used for local administration and follow-up of participants.

Statistical procedures in data processing will be to derive descriptive statistics for the distributions of each of the variables of interest, which will also be used to check for outlying observations and data errors. In addition, pairwise associations between variables of interest will be evaluated and possible errors will be checked with the local center and data values will be corrected where possible, or else coded as missing. Outlying observations that cannot be confirmed to be errors will be left as originally coded. Descriptive graphical and statistical methods at these early stages of analyses will include histograms, scatter plots and cumulative frequency distributions, one-way and two-way tables with appropriate percentages, Pearson's $\chi 2$ and/or Fisher's exact test for association in contingency tables, t-tests and/or Wilcoxon Rank Sum test for comparison of numerical variables between two groups, and Pearson correlations and simple linear regression models. For continuous secondary outcomes (e.g., several parameters of respiratory function) the distribution of residuals of linear regression analyses will be evaluated for overall skew and systematic spread with the values of dependent variables of interest ("heteroscedasticity") as to derive appropriate transformations that remove skew and achieve approximate "homoscedasticity."

8.3 Planned analysis (STROBE 12a-d)

Statistical significance will be set at alpha ≤ 0.050. All statistical analyses will be performed using STATA (Version 14.1, StataCorp, Texas, USA), R (Version 3.2.1, The R Foundation for Statistical Computing) or SPSS (Version 18.0.3, IBM, Somers, NY, USA).

8.3.1 Descriptive analysis

Descriptive statistics involving demographic data, lesion characteristics, life style characteristics, medication and vaccination, partly mechanical ventilation dependency, smoking, respiratory muscle

training and physical exercise as well as primary and secondary outcome parameters will be presented as mean (standard deviation) and median (25% and 75% quartile) or frequency (binomial 95% confidence interval), where appropriate. Descriptive statistics will be provided for the overall sample as well as stratified for the two groups that are discriminated by the event of at least one event of pneumonia during the study period.

8.3.2 Advanced regression modelling of primary and secondary outcomes

General principles

Univariable and multivariable regression modelling will be used to evaluate the primary outcome and secondary outcomes. Multivariable modelling as compared univariable modelling will principally allow us to investigate relative contribution of different predictors (or risk factors) to the outcome of interest, while controlling for potential confounding by other factors. To evaluate and eliminate confounding stratified models may also be used. Multivariable models may further be used to examine effect modification (interaction) as well as mediation (intervening variables that are on the causal pathway between a predictor and the outcome of interest) (19). The choice of regression model will be determined by the nature of the primary outcome and secondary outcomes (e.g., multivariable ROC analysis for diagnostic accuracy; multiple regression models for continuous variables, logistic regression models for dichotomous variables, and flexible parametric survival models for mortality data) as described in detail below.

Dealing with the hierarchical data structure (i.e., repeated measures for participants nested within clinics or countries) will be a fundamental issue in RESCOM analyses. The most basic means of dealing with such structure is to use extensions of the regression models listed above that allow for clustering of outcomes between individuals in the same cohort. The most important aim of analyses that allow for hierarchical data structures is to ensure that standard errors of regression coefficients are valid (since these will be too small if hierarchical data structures are ignored). Hierarchical analyses of RESCOM data will mainly use random-effects regression models allowing for sources of heterogeneity that may arise at the group (and/or individual) level (19, 20).

Regression modelling of primary outcome

To evaluate the diagnostic accuracy of markers of lung function (particularly MIP) for predicting or excluding clinical pneumonia we will use contemporary receiver operating characteristic (ROC) analyses techniques that allow for adjusting of covariate effects (21). Such adjustments principally facilitate an unbiased estimate of pneumonia classification accuracy of potential marker(s) by controlling for the effects of other factors, such as for instance individual patient characteristics, disease traits, or site-specific features of measurement or diagnostic procedures. In case covariates affect discrimination (i.e., the ROC curve), nonparametric and parametric estimators have been proposed and implemented as to combine marker and covariate information in describing the improvement in discriminatory accuracy (21-23). Importantly, these methodologies thus also support the evaluation of adjusted ROC curves by individual patient characteristics (e.g., gender, age) or SCI characteristics (e.g., lesion level, lesion completeness, temporary or permanent artificial ventilation).

Regression modelling of secondary outcomes

Analyses of secondary outcomes will make use of common regression models, or extensions of these models. The choice of regression model will be determined by the statistical nature of the secondary outcome variable, in particular its error distribution (19). We thus anticipate using multiple regression for the modelling of the lung parameters MIP, MEP, FVC, FEV_1 and PEF, if needed using appropriate transformations as to meet normality assumptions. In case a normal error distribution is not achieved,

the outcome variable will be converted into a ordinal variable with multinomial categorical outcomes using clinically-relevant cut-offs and analysed using ordinal regression or stereotype regression, the latter in case of failure to meet proportional odds assumptions (24-26). Alternatively, a binary cut-off combined with logistic regression analysis may be used.

For the analysis of all-cause and pneumonia-related mortality flexible parametric survival models will be applied that allow for a flexible approach in modelling and estimation of the baseline hazard of death (27, 28). Survival time will start at the date of initiation of first rehabilitation and censoring is at date of discharge from local first rehabilitation or at date of death. The analysis of pneumonia-related mortality will be adjusted for competing risks, i.e., events that either hinder the observation of the event of interest or modifies the chance that this event occurs. Potential competing risks for the event of pneumonia-related mortality during first SCI rehabilitation for instance include other causes of mortality (e.g., septicaemia, neoplasm) or transfer to another rehabilitation clinic or another facility to receive specialized treatment. In such cases the censored time-to-events reflect a form of incomplete data that may induce bias in estimates of pneumonia risk from unadjusted analyses. Competing risk analysis accounts for competing events as to provide an unbiased estimate of the pneumonia-related hazard of death during first rehabilitation (29, 30).

Predictors; extraneous, mediating, moderating and confounding variables

The main predictors (exposures of interest) in the modelling of the primary outcome and secondary outcomes include the degree of motor and sensory neurological impairment as captured by the ASIA Impairment Scale (35); lesion level classified as paraplegia or tetraplegia; PCF and partial dependency on mechanical ventilation (a minimum of 1hour free of ventilator dependency during the day). Further predictors for secondary outcomes include an index of physical activity as well as an indicator for respiratory training, assessed using a questionnaire.

Likely extraneous variables (affecting either the exposure or the outcome) or confounding variables (affecting both the exposure and the outcome) comprise gender; age at start of rehabilitation; time since SCI. Further variables include smoking status (current smoker, former smoker, non-smoker), and pack-years; individual medication use and vaccination (particularly against influenza); and also influenza activity in the local community. Some variables may also induce mediating effects, which can be evidenced by targeted mediation analysis, or cause moderating effects, which can be verified by investigating interaction terms with specific predictor variables. In defining the actual modelling strategy, which particularly includes accounting for extraneous and confounding variables in the estimation of effect sizes for predictor variables, we will make use of the graphical software DAGitty (31).

Continuous variables, such as age and time since injury, may show a nonlinear relationship with the primary outcome or secondary outcomes. To formally evaluate and model nonlinear associations for these variables we will use multivariable fractional polynomial regression as well as piecewise/spline regression techniques in the modelling of survival time (27, 32).

Handling of sampling bias and attrition bias

As any observational study in a clinical setting, RESCOM may suffer from sampling bias, implying that the study population is not a random selection from the target population. Furthermore, attrition bias may occur, implying the selective dropout of study participants. Various factors may principally account for sampling bias as well as attrition bias, including the subjects' cultural background, gender, age, or socioeconomic status.

Descriptive and statistical approaches to evaluate and counteract sampling or attrition bias:

- Comparative descriptive analysis of baseline characteristics of eligible population that was initially invited to participate to the study with effective study participants. If appropriate, use of inverse probability weighting (derived from propensity scores for study participation) in weighted regression analysis
- Evaluation of selective attrition in relation to baseline characteristics. Again, inverse probability weighting for longitudinal studies can be used to counterweigh potential developing attrition bias in regression analysis.

8.3.1 Datasets to be analysed

Regression analyses of the primary outcome and secondary outcomes may suffer from missing data, which may cause bias and loss of information in analyses that are restricted to study participants with complete data ("complete-case analyses"). To appropriately account for missing data in advanced regression analyses we will use multiple imputation techniques as well as an iterative imputation method (missForest) based on a random forest (33, 34).
Due to the relatively high anticipated sample size, the analysis will be split up into specific sub-groups (e.g. completeness of lesion, para-/tetraplegia, type of pneumonia). For mortality flexible parametric modeling of survival data) and other secondary outcome analyses will be performed Handling of missing data

8.3.2 Ancillary analysis

For primary outcome: if distribution of ROC is not normal, a non-parametric approach can be used as part of sensitivity analysis (Pepe 2013).

Further, a comparison of results from imputed data (main analysis) with results of unimputed data (i.e, including complete data sets only) will be performed.

8.3.3 Deviations from the original statistical plan

The analysis protocol will be updated accordingly if needed.

9. DATA AND QUALITY MANAGEMENT

(HRO Art. 5, 25-27, Annex 2/1.7)

9.1 Data handling and record keeping / archiving (HRO Art. 5, 26, 27, Annex 2/1.7)

The secuTrial© data management system (iAS, Berlin, Germany), a web-based data capture and management system, will be used. The system is hosted on a server of the Swiss Paraplegic Centre.
The project set-up and eCRFs will be tested by the Data Manager of the Swiss Paraplegic Center, Clinical Trial Unit prior to the release into the productive environment using a custom testing protocol.
Every staff member is authorized for any CRF entry and by initials noted on the CRF the investigator can be subsequently identified. The data on the CRF will later be entered in the secuTrial© database (iAS, Berlin, Germany).

One person will enter the data from the CRF paper form into the secuTrial© database. A second person will control the correctness of the data in the secuTrial© and the principal investigator will finally release the data for archival storage.
The Clinical Trial Unit will only give access to 2 people: Person A will get access for data entering and controlling and the local investigator (Person B) for data release.
Plausibility rules will be established in the data capture system to promote data quality. Furthermore, data will be reviewed and verified prior to data entry completion.
Encrypted data will be exported from the data management system for analysis in statistic software.

9.2 Confidentiality, Data Protection (HRO Art. 5)

Project data will be handled with uttermost discretion and only be accessible to authorised personnel. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections. The data management system allows to define roles for data entry, verification, validation and management. An audit trail documents all entries and changes made in the system and by whom.
Personal data of participating subjects which allow to identify an individual, will not be stored on a server or personal computer, nor will any names of subjects be transmitted to the main study center in Nottwil. These data will be printed on paper and stored in a locked data storage room with limited access in each participating center. An anonymous identification number will allow to connect the data entered in the system, but only by each center for their own subjects. Only anonymous data will be stored in the electronic data capture and management system. Encrypted data will be exported from the data management system for analysis in statistic software.

For data verification purposes, authorised representatives of a competent authority (e.g. an ethics committee) may require direct access to parts of the medical records relevant to the project, including participants' medical history.

9.3 Coding (HRO Art. 25-27)

The secuTrial© (iAS, Berlin, Germany), a web-based data capture and management system, will be used. The system is hosted on a secure hospital server. Personal data, which allows to identify an individual, will not be stored on a server or personal computer. These data will be printed on paper and stored in a locked data storage room with limited access in each single site where the data are assessed. An anonymous identification number will allow to connect the data entered in the system with an individual. Only anonymous data will be stored in the electronic data capture and management system.

9.4 Archiving and Destruction

During the study the respective data will be archived in each single study site on paper and as electronic data in the Swiss Paraplegic Centre Nottwil.
During the course of the study, the individuals mentioned in this application will have access to the data according to their pre-defined roles. After termination of the study and archiving of the data, only the Principal Investigator and secuTrial© Data Manager will have access to the data. The Data Manager will only have access to the encrypted data.
A back-up system is set in place. It is maintained and controlled by the IT department of the Swiss Paraplegic Centre. Electronic data will be stored in an electronic archive maintained and controlled by the IT department of the Swiss Paraplegic Centre. Electronic data will not be deleted. Source data and

identification data will be stored in a locked archive room with limited access for a minimum of 15 years.

10. PUBLICATION AND DISSEMINATION POLICY

(HRO Art. 15j; STROBE 22; HRO Annex 2/1.10)

10.1 Publication of results

The plans are to write three papers about the topic "Inspiratory muscle strength and respiratory complications after spinal cord injury: a multicenter, prospective cohort study" in 2019 and publish the results in peer reviewed journals. The main topics of these papers should focus on:

- Diagnostic accuracy of inspiratory muscle strength for prediction of pneumonia
- Mortality due to pneumonia and associated factors
- Determinants of pneumonia after SCI (multivariate modelling)

The results can be presented in different conferences e.g. dmgp or ISCoS. The authorship will be arranged in advance as follows, the first author on the publications will be Mrs Anja Raab and the senior author will be Mrs Gabi Müller. Other persons with substantial contributions will be mentioned in-between according to guidelines for publishing of the selected journal. The publications will be also used for obtaining a PhD-degree (Anja Raab).
Local investigators will be included in the discussion of results and publication process of all publications from this project. All local investigators will co-author all publications from this project and therefore will all have to approve at least the last version of every publication.

10.2 Data sharing

In general, only the study investigators have access to the full study dataset in order to ensure that the overall results are not disclosed by an individual study site prior to the main publication. Site investigators are allowed to access the full dataset if a formal request describing their plans is approved by the study investigators. All local data belong to the local centers and will only be transferred coded to the study center.

11. FUNDING AND SUPPORT

(HRO Art. 15j; STROBE 22; HRO Annex 2/1.10)

The main financial support (210'000.- Euro) for the project will be given from the Foundation "Wings for life", Salzburg, Austria.

Wings for life
Address: Fürstenallee 4, 5020 Salzburg, Austria
Email: office@wingsforlife.com
Phone: +43 (0)662 6582-4244
Fax: +43 (0)662 6582-4265

Additionally, this project is also a "nested project" of the SwiSCI cohort study of the Swiss Paraplegic Research. Therefore, parts of the costs for the Swiss Centers of the study will be covered by a 'SwiSCI-Nested project Start-up Grant' (43'000.- SFr.) from the Swiss Paraplegic Research.

12. INSURANCE

(HRO Annex 1; HRO Annex 2/1.6)

n.a.

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14. APPENDICES

none