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Respiratory function and respiratory complications in spinal cord injury: protocol for a prospective, multi-center cohort study in high income countries.

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Protocol of the RESCOM study

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ABSTRACT

Introduction: Pneumonia is one of the leading complications and causes of death after a spinal cord injury (SCI). After a cervical or thoracic lesion, impairment of the respiratory muscles decreases respiratory function, which increases the risk of respiratory complications. Pneumonia substantially reduce patient's quality of life, prolong inpatient rehabilitation time, increase health care costs, or at worse, lead to early death. Respiratory function and coughing can be improved through various interventions after SCI, but the available evidence as to which as aspect of respiratory care should be optimized is inconclusive. Further, ability of respiratory function parameters to predict pneumonia risk is insufficiently established. This paper details the protocol for a large-scale, multicenter research project that aims to evaluate the ability of parameters of respiratory function to predict and understand variation in inpatient risk of pneumonia in SCI.

Methods and analysis: RESCOM, a prospective cohort study, began recruitment in October 2016 across 10 SCI rehabilitation centers from Australia, Austria, Germany, the Netherlands and Switzerland. In-patients with acute SCI, with complete or incomplete cervical or thoracic lesions, 18 years or older and not dependent on 24-hour mechanical ventilation are eligible for inclusion. The target sample size is 500 participants. The primary outcome is an occurance of pneumonia; secondary outcomes include pneumonia-related mortality and quality of life. We will use the longitudinal data for prognostic models on inpatient pneumonia risk-factors.

Ethics and dissemination: The study has been reviewed and approved by all local ethics committees of all participating centers. Study results will be disseminated to the scientific community through peer-reviewed journals and conference presentations, to the SCI community, other stakeholders and via social media, newsletters and engagement activities.

Registration details: ClinicalTrials.gov NCT02891096

Keywords: 1. spinal cord injury 2. respiratory muscle strength 3. pneumonia

ARTICLE SUMMARY

Strengths and limitations of this study

- RESCOM (for RESpiratory COMplications) is the first multinational study to prospectively evaluate predictors of pneumonia from a representative sample of persons with spinal cord injury (SCI) receiving inpatient rehabilitation in a high-income setting.

- The RESCOM cohort will enroll 500 persons with SCI to develop generalizable prognostic models as well as to validate causal risk factors, specifically impaired respiratory function, of pneumonia risk.

- Because respiratory function following SCI may be improved through respiratory muscle training, study results may inform and improve current clinical practice and patient management through the better targeting of interventions.

- Generalizability of the study with respect to pneumonia risk is limited to patients with less than 24 hours of mechanical ventilation because respiratory function cannot be measured using standard techniques in those who are intubated, as well as patients with a poor general health status or facing other severe secondary morbidity may not consent to study participation or may not participate in all of the measurements over time.

INTRODUCTION

Pneumonia is a leading complication and cause of death after a spinal cord injury (SCI), even in high income countries.[1 2] In newly injured patients, pneumonia may substantially complicate and lengthen the period of first rehabilitation, while community dwelling persons living with SCI are commonly re-hospitalized for pneumonia over extended periods that frequently involve intensive care.[3 4]

Contemporary health care policy and patient management aims to improve health-related quality of life and life expectancy in the SCI community as well as to reduce infection-related health care costs. Reducing the incidence of pneumonia is therefore a major objective. Critical to this goal is that 1) persons with an elevated risk of pneumonia can be identified early (prediction), 2) modifiable risk factors are known (causality) and readily measurable, and 3) effective interventions targeting key risk factors are established. Unfortunately however, the contemporary evidence base regarding risk groups and modifiable risk factors of pneumonia in SCI, and subsequent effective intervention strategies, remain scant.[5-8] Most existing studies evaluating between-person differences in risk of pulmonary complications assessed non-modifiable factors only; demographics (sex, age), injury severity (level, completeness) or spinal shock severity.[5 6 8]

Impairment of respiratory function represents the most promising target for clinically relevant research on pneumonia in SCI, as these measures are directly linked to the neurological impairment and appear to be modifiable through targeted respiratory training.[9-11] Respiratory muscles below the level of injury may become paralyzed or impaired [12] and respiratory function is compromised with higher levels of injury causing greater impairment.[9] [13] Cough impairment is also considered critically important, as insufficient removal of airway secretion may result in the development of mucus plugging and complications such as atelectasis or pneumonia.[14] [15] Effective coughing comprises an inspiration, compression and expulsion phase. Cough impairment following SCI may affect each phase due to the weakening of inspiratory and expiratory muscle function, which may decrease the maximum volume of expelled air by restricting both the maximum inspiratory volume prior to contraction as well as a reduction in the amount able to be expelled.[14] [16] The limited evidence in SCI suggests that inspiratory (using maximal inspiratory muscle pressure; PI_{max}) rather than expiratory function (maximal expiratory muscle pressure; PE_{max}) is the prime determinant of cough capacity (peak flow), particularly in patients with a motor-complete cervical SCI.[17] Postma et al. found that impaired pulmonary function may

increase respiratory infections at one year after SCI, but their study did incorporate respiratory muscle strengthening and respiratory complications were incompletely assessed.[7]

To the best of our knowledge, there is currently no comprehensive database available for the further development of generalizable prognostic models, nor to improve causal inference of pneumonia risk in light of impairment in respiratory function. The multicenter and multinational cohort study RESCOM aims to establish such an evidence base in SCI. We believe RESCOM will thereby improve clinical practice through better targeting of interventions during the inpatient setting in high-income countries.

METHODS AND ANALYSES

Design and setting

RESCOM is a prospective international, multi-center cohort study in high income countries. Data collection commenced in October 2016 across 10 specialized rehabilitation centers for SCI from Austria (2 centers), Australia (1 center), Germany (1 center), The Netherlands (2 centers) and Switzerland (4 centers) and is still ongoing.

Study population

Newly injured persons who are aged 18 years or older, admitted for inpatient rehabilitation in the participating centers, with complete or incomplete lesions (grades A-D on the American Spinal Injury Association Impairment Scale (AIS) [18] and cervical or thoracic lesion levels (right and left motor level between C1- T12). Persons with severe pre-existing scoliosis, progressive neurological diseases, 24h mechanical ventilation dependency until more than 3 months post injury or severe mental disorders are excluded.

Sample Size

A retrospective study in one of the Swiss participating centers indicated good discriminatory power for key dimensions of respiratory muscle strength based on a total number of 110 episodes of pneumonia.[19] To meet the study purposes for RESCOM we estimated the cumulative number of pneumonia events at 100. The minimal adequate sample size to observe 100 pneumonia cases was calculated by applying RESCOM inclusion criteria to the inception cohort of the Swiss Spinal Cord

Injury (SwiSCI) study. A minimal sample size of 500 was required to observe a pneumonia prevalence rate of 20% in the SwiSCI cohort.[20]

Procedures

The measurement schedule of RESCOM includes up to four measurement time-points (T1-T4) during the inpatient rehabilitation period (Figure 1). Following start of rehabilitation, newly injured patients are contacted for recruitment at about 4 weeks (T1) or at 12 weeks (T2) if the first six or more weeks following injury were spend on the ICU or in a general hospital for acute care. Subsequent assessments are planned at 24 weeks (T3) and at discharge to the community (T4). The T4 timepoint may precede and replace T2 and/or T3 in patients with a shorter length of inpatient rehabilitation stay. Temporal start and length of inpatient stay for rehabilitation varies with injury severity, general health status of patients and between countries and clinics. As such, between two and four measurement time-points are anticipated across patients, with those with more severe lesions and the longest length of stay providing more time points. In the four Swiss centers RESCOM is run as a "nested project" of the Swiss Spinal Cord Injury (SwiSCI) cohort study (www.swisci.ch).[20] The temporal schedule of data collection of RESCOM is aligned to that of SwiSCI and the relevant data for RESCOM will be extracted from the SwiSCI database additionally to RESCOM specific measurements and questionnaires.

Quality control

Each of the participating centres has one or two responsible study nurses. Before the start of recruitment, a study nurse meeting in the Swiss Paraplegic Centre Nottwil was performed to train all study nurses for the procedures and the assessments of the study. A study manual has been established to give an overview of the procedures and all assessed variables. A frequently asked question sheet is available in the study specific database (secuTrial®, iAS, Berlin, Germany) with all relevant questions the study nurses asked during data collection. For quality control of data assessment, regular central (database secuTrial®) and one local monitoring visit in each of the participating centers are performed. The coordinating study center supports one central study coordinator who is responsible for central and local monitoring as well as for support of the local study nurses for questions concerning patient inclusion, data collection and entry into the database.

Parameters assessed

Primary outcome

The occurance of pneumonia is the primary outcome of RESCOM, observed during the risk period of interest from time of injury until the end of inpatient rehabilitation. Medical records of inpatients are screened for diagnosis of pneumonia, including records from the acute care phase before admission to the rehabilitation center where available. Pneumonia is classified by type and cause, and the date of onset and duration of each event isrecorded. Pneumonia is clinically diagnosed using the criteria described in the pneumonia flow diagram as endorsed by the Center for Disease Control and Prevention (CDC).[21] Mortality is defined as pneumonia-related, if pneumonia was clinically recorded as the initiating cause of events leading to death. Other causes of death are similarly classified.

Participant characteristics

All participant characteristics are obtained from medical records. Basic characteristics that are collected at T1 include gender, age, height, cause of SCI (traumatic or non-traumatic) and smoking history. Parameters that may temporally vary, including body weight, motor lesion level and American Spinal Injury Association Impairment Scale (AIS), medication, frequency of defecation as well as medical complications are assessed on all available measurement time-points. At T4, the actual smoking status and ICD-10 coded co-morbidities are recorded additionally.

Additional parameters

Additional parameters assessed at all measurement time-points, i.e. up to four times per participant:

- Measurement of respiratory muscle strength and lung function
- ISCoS Pulmonary function data set [22]
- Quantiative questionnaire on physical exercise training
- Quantitative questionnaire on respiratory therapy and respiratory muscle training
- Bogenhausener Dysphagia score (BODS)
- ISCoS Quality of Life questionnaire [23]

Measurement of respiratory function

Measurement of respiratory function consists of respiratory muscle strength (maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max})) and lung function with forced vital capacity

(FVC), forced expiratory volume in 1s (FEV_1), peak expiratory flow (PEF) and peak cough flow (PCF). All measurements are performed at the same day according to the ATS/ERS guidelines [24] in a sitting position either in the participant's own wheelchair or on a chair in participants that are able to walk. To derive a reliable estimate of the highest value for each parameter, each measurement is repeated until the three highest values of a given parameter are within a 20% range. The highest value of each parameter is retained for further analysis.[25]

Measurement of respiratory muscle strength and lung function have been harmonized across the 10 centers using identical equipment. PI_{max} and PE_{max} are measured using a hand-held respiratory pressure meter (Micro RPM, Micro Medical, Hoechberg, Germany). The PI_{max} measurement is derived from residual volume and PE_{max} from total lung capacity, against the occluded one-way valve of the respiratory pressure meter with the pressure maintained for at least one second. To derive the maximum pressure over a one second period, the patient is instructed to maintain in- and expiratory pressure for at least 1.5 seconds.[26] Abdominal binders are removed prior to any measurement of respiratory function.[27]

The FVC is the total volume of air the participant is able to exhale after a maximal inspiration. The FEV_1 is the total volume of air that has been exhaled at the end of the first second of maximal forced expiration. PEF is the maximum flow of air achieved during the maximum expiratory flow manoeuver. [28] During the PCF manoeuver the maximum flow of air is measured by having the participant cough as forcefully as possible through a peak flow meter. Participants breathe through a mouthpiece while wearing a nose clip. Across study centers, lung function parameters are measured accordingly, but using three different brands of portable spirometer, including Micro Loop® (Care Fusion, Basingstoke, UK; all Swiss, Dutch and German centers), EasyOne Spirometer® (Niche Medical, Melbourne, Australia; Australian center), Masterscreen PFT Pro® (Care Fusion, Hoechberg Germany; one Austrian center) and Vitalograph® (Ennis, Ireland; one Austrian center).

ISCoS Pulmonary function data set

The ISCoS Pulmonary function data set [22] consists of questions on pulmonary complications (asthma, chronic obstructive pulmonary disease, sleep apnea and others) before and after SCI, smoking history, current utilization of pulmonary assistance and lung function measurement.

Questionnaires on physical exercise and respiratory muscle training as well as on respiratory therapy

The questionnaires on individual respiratory muscle training, regular physical exercise and therapy are kept as simple as possible. Only quantitative or yes/no questions on physical activities performed during the last seven days are asked. Physical activity, duration of sport activities as well as number of physiotherapy sessions per week are recorded. Respiratory therapies such as mobilisation of secretion, manual blowing or air stacking and in-/exsufflation are assessed on a yes/no basis and if yes, whether with or without manual cough assistance. Respiratory muscle training is assessed separately for in- and expiratory muscle strength training as well as respiratory muscle endurance training (i.e. isocapnic hyperpnoea). In case of training, the name of the device, the number of training sessions per week, the number of repetitions per session as well as the resistance is noted.

Bogenhausener Dysphagia score (BODS)

Dysphagia is assessed using the Bogenhausener Dysphagia score (BODS), which consist of two scales, each with a score from 1 to 8, resulting in a sum-score of 2 to 16. The first scale quantifies swallowing of saliva and whether the patient has a tracheal cannula. For patients with tracheal cannula, the degree of blocking is quantified as fully, partly or mainly not blocked. The second scale quantifies problems with oral ingestion including four of the eight scores for parenteral nutrition. The BODS is assessed by a speech therapist or a physiotherapist, in close coordination with the RESCOM study nurse.

ISCoS quality of life questionnaire

Quality of Life (QoL) is evaluated using the ISCoS QoL questionnaire.[23] This measurement instrument accepts a multi-facetted concept and includes three questions that capture general QoL (overall well-being), rating of physical health, and satisfaction with psychological health.

Database secuTrial®

To enable secure capture and management of RESCOM data, the professional and web-browser based database system secuTrial® is used. SecuTrial® fulfills the minimal requirements for data storage and management indicated in the ICG-GCP guidelines and also supports the central monitoring of data collection across all participating centers. Database set-up, personal accounts with

pre-defined roles for all study collaborators as well as support, data export and archiving is provided by a study-independent database manager from the study-center in Nottwil, Switzerland.

Methods of minimizing bias

Study participants receive an introduction for the study procedure by the local study nurse skilled in the management of persons with SCI and trained for all study specific tasks. A standardized study protocol was defined to minimize attrition bias.

The coding of the participants is conducted by the study nurses of each site in order to keep the data management and the biostatistician blinded (de-identified at source). The coding list remains with the study nurses of each site for the whole duration of the study and archiving period. Thus, coding is conducted without any influence of the principal investigator, the data manager or biostatistician. The study investigators strive for complete separation of the persons involved in the steps of enrolment and data collection from those involved in the data management and analysis.

All assessments are conducted and entered into the study database by the trained study nurse(s) of each participating center.

Statistics

Statistical analysis will involve basic descriptive statistics and multivariable regression analyses that take into account the longitudinal and multilevel structure of the data. A global overview of the multivariable data analysis plan for investigating the association between respiratory function and pneumonia is given in Figure 2. To evaluate variation in pneumonia risk, time-to-event analysis techniques (e.g., flexible parametric survival modeling) will be employed, taking date of injury as the starting point of the risk period. Regression models targeting causal inference will make use of time-updated information for all variables in accordance with the repeated measurement schedule of RESCOM, while controlling for between-person and between-center sources of variance using random and fixed effects. The exposure 'respiratory function' will be operationalized using parameters of respiratory muscle strength and parameters of lung function, as a latent construct within generalized latent variable modeling or as individual parameters in selected analysis as required.[29] Critical confounders that have been defined using evidence from the literature and expert opinion of RESCOM collaborators include age, lesion severity, time since injury (structurally captured in time-to-event modelling), artificial ventilation and medication. Models targeting prognosis of pneumonia during first

rehabilitation will only include parameters of respiratory function that have been collected at baseline.[30 31]

ETHICS AND DISSEMINATION

Full ethical approval for this project has been obtained by all local ethics committees of all participating centers. We certify that all applicable institutional and governmental regulations concerning the ethical use of data of human volunteers are followed during the course of this research.

Potential protocol modifications and amendments will be submitted to the ethical committees for approval. This project has been registered with ClinicalTrials.gov NCT02891096 and regular study updates are presented on Research Gate (https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury).

All participants give written or witnessed verbal consent if upper limb function is too impaired for a participant to sign, prior to entering the study.

The study results will be disseminated through publication in scientific journals, presentation at relevant conferences, directly to the participants and clinicians as well as on social media and in newsletters. The dissemination aims to provide clinicians with reliable prognostic factors to identify persons who are at heightened risk of pneumonia and thus, to effectively reduce pneumonia risk and pneumonia-related hospitalizations.

STRENGTH AND LIMITATIONS

RESCOM is the first prospective, international study that reports modifiable predictors of pneumonia from a representative sample of persons with SCI during inpatient rehabilitation. Its comprehensive evidence base facilitates the systematic evaluation of the discriminatory power of respiratory function parameters for pneumonia risk in high income countries.

The RESCOM study is effective in recruiting a representative sample of inpatients with a motor complete or incomplete SCI in Austria, Australia, Germany, The Netherlands and Switzerland. The anticipated minimal sample size of 500 should provide project sufficient statistical power to answer the key hypothesis that respiratory function, and PI_{max} in particular, is a strong prognostic parameter that quantifies clinical pneumonia risk in SCI. The longitudinal, international design of this project is considered a further strength; participants can be observed during the whole period of inpatient rehabilitation in different countries. Various factors like a central web-based database, a study nurse

meeting, a comprehensive study manual and regular monitoring were implemented to ensure the standardization of the measurements and data and thus to keep quality of the project in the 10 centers as high as possible.

For data collection we used the International SCI Core Data Set, [32 33] the International SCI QoL Basic Data Set [23] and the International SCI Pulmonary Function Data Set [22] which are developed to provide global data standards for SCI clinical research. The advantage of using these standardized data sets is to increase the data quality and to facilitate data sharing.

Potential limitations include the observational nature of the project which limits causal inference even within a prospective study design. Although the RESCOM sample reflects the composition of the source population quite well, we cannot exclude potential selection bias and therefore, the results of the RESCOM project may not be transferable to all persons with SCI. There is a risk that the study inclusion and exclusion criteria may miss those patients with a potential high risk of pneumonia because those with more severe lesions or more complications may not consent to participate in an observational study that may not directly increase their outcome. Similalry, patients with a very long stay in the intensive care unit or a very late admission to the rehabilitation unit, may miss T2 and therefore no more qualify for study participation. Those patients with 24h of mechanical ventilation are excluded since respiratory function cannot be measured and also those with other languages than used in our study centers are excluded. Another limitation of this project is that we do not have a follow-up period after the participants complete inpatient rehabilitation.

In summary, using discriminatory parameters of respiratory function, clinicians may identify persons with SCI who are at heightened risk of developing pneumonia during inpatient rehabilitation. Thus, interventions can be targeted at these persons to reduce pneumonia risk. The RESCOM study is well-positioned to determine prognostic parameters of respiratory function for pneumonia risk in SCI.

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Collaborators

This study offers options of scientific collaborations.

Author Contributions

GM is the principal investigator of the RESCOM project. AMR and GM designed the study and AMR, MWGB and GM wrote a first draft of this manuscript. AMR is responsible for the monitoring-visits. All authors worked on, reviewed and approved the final version of the manuscript.

Data Availability Statement

After completion of data collection and analysis, all relevant data and stimates of ths study will be deposited on Dryad.

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Competing Interests

The authors declare no conflict of interest.

Patient consent

Obtained.

Registration

Further details about the study can be found under ClinicalTrials.gov NCT02891096 and regular study updates are presented on Research Gate (https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury).

Ethics approval: Approved by all local ethics committees of all participating centers.

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FIGURE LEGENDS

Figure 1

Time frames for measurements (T1 toT4) during inpatient rehabilitation. T1-T3 time-windows with days post injury (dpi) are shown by blue bars and T4 by the green bar above.

Figure 2

Global scheme of the planned data analysis investigating the dynamic association between respiratory function and pneumonia. In regression modelling all variables will be time-updated in accordance with the repeated measurement schedule of RESCOM and controlling for between-person and between-center sources of variance. Respiratory function is operationalized using parameters of respiratory muscle strength and parameters of lung function.

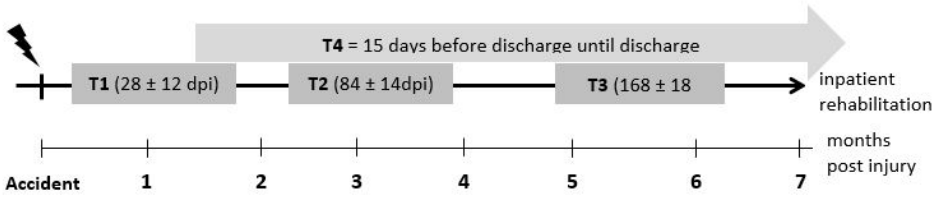

Figure 1
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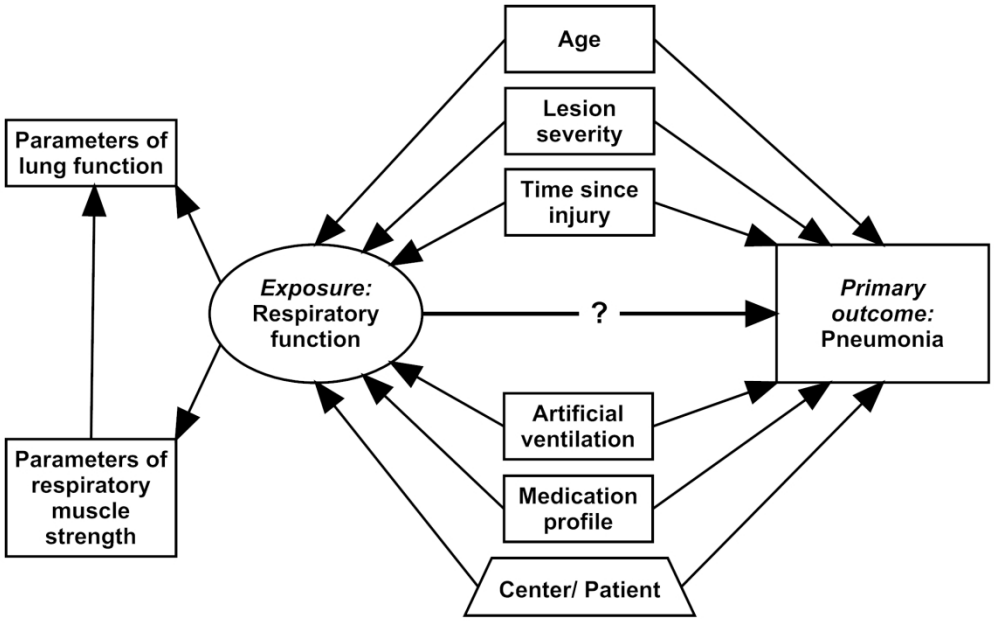

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6/7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6/7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11/Fig.2
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a. since this is a protocol paper
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n.a. since this is a protocol paper
		(b) Indicate number of participants with missing data for each variable of interest	

		(c) Summarise follow-up time (eg, average and total amount)	n.a. since this is a protocol paper
Outcome data	15*	Report numbers of outcome events or summary measures over time	n.a. since this is a protocol paper
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a. since this is a protocol paper
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a. since this is a protocol paper
Discussion			
Key results	18	Summarise key results with reference to study objectives	n.a. since this is a protocol paper
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12/13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n.a. since this is a protocol paper
Generalisability	21	Discuss the generalisability (external validity) of the study results	12/13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Respiratory function and respiratory complications in spinal cord injury: protocol for a prospective, multi-center cohort study in high income countries.

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Respiratory function and respiratory complications in spinal cord injury: protocol for a prospective, multi-center cohort study in high income countries.

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Running title

Protocol of the RESCOM study

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ABSTRACT

Introduction: Pneumonia is one of the leading complications and causes of death after a spinal cord injury (SCI). After a cervical or thoracic lesion, impairment of the respiratory muscles decreases respiratory function, which increases the risk of respiratory complications. Pneumonia substantially reduces patient's quality of life, prolong inpatient rehabilitation time, increase health care costs, or at worse, lead to early death. Respiratory function and coughing can be improved through various interventions after SCI, but the available evidence as to which as aspect of respiratory care should be optimized is inconclusive. Further, ability of respiratory function parameters to predict pneumonia risk is insufficiently established. This paper details the protocol for a large-scale, multicenter research project that aims to evaluate the ability of parameters of respiratory function to predict and understand variation in inpatient risk of pneumonia in SCI.

Methods and analysis: RESCOM, a prospective cohort study, began recruitment in October 2016 across 10 SCI rehabilitation centers from Australia, Austria, Germany, the Netherlands and Switzerland. In-patients with acute SCI, with complete or incomplete cervical or thoracic lesions, 18 years or older and not/no more dependent on 24-hour mechanical ventilation within the first three months post injury are eligible for inclusion. The target sample size is 500 participants. The primary outcome is an occurance of pneumonia; secondary outcomes include pneumonia-related mortality and quality of life. We will use the longitudinal data for prognostic models on inpatient pneumonia risk-factors.

Ethics and dissemination: The study has been reviewed and approved by all local ethics committees of all participating centers. Study results will be disseminated to the scientific community through peer-reviewed journals and conference presentations, to the SCI community, other stakeholders and via social media, newsletters and engagement activities.

Registration details: ClinicalTrials.gov NCT02891096

Keywords: 1. spinal cord injury 2. respiratory muscle strength 3. pneumonia

ARTICLE SUMMARY

Strengths and limitations of this study

- RESCOM (for RESpiratory COMplications) is the first multinational study to prospectively evaluate predictors of pneumonia from a representative sample of persons with spinal cord injury (SCI) receiving inpatient rehabilitation in a high-income setting.
- The RESCOM cohort will enroll 500 persons with SCI to develop generalizable prognostic models as well as to validate causal risk factors, specifically impaired respiratory function, of pneumonia risk.
- Because respiratory function following SCI may be improved through respiratory muscle training, study results may inform and improve current clinical practice and patient management through the better targeting of interventions.
- Generalizability of the study with respect to pneumonia risk is limited to patients with less than 24 hours of mechanical ventilation within the first three months post injury, because respiratory function cannot be measured using standard techniques in those who are intubated.
- This study will provide insight whether the improvement of respiratory muscle strength and respiratory function represent promising targets for intervention to reduce pneumonia risk following spinal cord injury.

INTRODUCTION

Pneumonia is a leading complication and cause of death after a spinal cord injury (SCI), even in high income countries.[1 2] In newly injured patients, pneumonia may substantially complicate and lengthen the period of first rehabilitation, while community dwelling persons living with SCI are commonly re-hospitalized for pneumonia over extended periods that frequently involve intensive care.[3 4]

Contemporary health care policy and patient management aims to improve health-related quality of life and life expectancy in the SCI community as well as to reduce infection-related health care costs. Reducing the incidence of pneumonia is therefore a major objective. Critical to this goal is that 1) persons with an elevated risk of pneumonia can be identified early (prediction), 2) modifiable risk factors are known (causality) and readily measurable, and 3) effective interventions targeting key risk factors are established. Unfortunately however, the contemporary evidence base regarding risk groups and modifiable risk factors of pneumonia in SCI, and subsequent effective intervention strategies, remain scant.[5-8] Most existing studies evaluating between-person differences in risk of pulmonary complications assessed non-modifiable factors only; demographics (sex, age), injury severity (level, completeness) or spinal shock severity.[5 6 8] Only one recent study investigated modifiable risk factors for pneumonia, i.e. steroid administration, which may be helpful to maintain muscle mass and strength but may also cause other relevant side-effects.[9]

Impairment of respiratory function represents the most promising target for clinically relevant research on pneumonia in SCI, as these measures are directly linked to the neurological impairment and appear to be modifiable through targeted respiratory training.[10-12] Respiratory muscles below the level of injury may become paralyzed or impaired [13] and respiratory function is compromised with higher levels of injury causing greater impairment.[10 14] Cough impairment is also considered critically important, as insufficient removal of airway secretions may result in the development of mucus plugging and complications such as atelectasis or pneumonia.[15 16] Effective coughing comprises an inspiration, compression and expulsion phase. Cough impairment following SCI may affect each phase due to the weakening of inspiratory and expiratory muscle function, which may decrease the maximum volume of expelled air by restricting both the maximum inspiratory volume prior to contraction as well as a reduction in the amount able to be expelled.[15 17] The limited evidence in SCI suggests that inspiratory (using maximal inspiratory muscle pressure; PI_{max}) rather than expiratory

function (maximal expiratory muscle pressure; PE_{max}) is the prime determinant of cough capacity (peak flow), particularly in patients with a motor-complete cervical SCI.[18] Postma et al. found that impaired pulmonary function may increase respiratory infections at one year after SCI, but their study did incorporate respiratory muscle strengthening and respiratory complications were incompletely assessed.[7]

To the best of our knowledge, there is currently no comprehensive database available for the further development of generalizable prognostic models, nor to improve causal inference of pneumonia risk in light of impairment in respiratory function. The multicenter and multinational cohort study RESCOM aims to establish such an evidence base in SCI. We believe RESCOM will thereby improve clinical practice through better targeting of interventions during the inpatient setting in high-income countries.

METHODS AND ANALYSES

Design and setting

RESCOM is a prospective international, multi-center cohort study in high income countries. Data collection commenced in October 2016 across 10 specialized rehabilitation centers for SCI from Austria (2 centers), Australia (1 center), Germany (1 center), The Netherlands (2 centers) and Switzerland (4 centers) and is still ongoing.

Study population

Newly injured persons who are aged 18 years or older, admitted for inpatient rehabilitation in the participating centers, with complete or incomplete lesions (grades A-D on the American Spinal Injury Association Impairment Scale (AIS) [19] and cervical or thoracic lesion levels (right and left motor level between C1- T12). Persons with severe pre-existing scoliosis, progressive neurological diseases, 24h mechanical ventilation dependency until more than 3 months post injury or severe mental disorders are excluded.

Sample Size

For the analysis of pneumonia risk we estimated, over a conservative range of pneumonia event probabilities from 0.1 to 0.2, the minimal sample size needed to detect a plausible hazard ratio (effect

size of interest) of 1.7 or more for inspiratory muscle strength (principal predictor variable).[20] Using a conventional power of 0.8 and significance level of 0.05, this analysis indicated a sample size of 500 as adequate for the purpose of the present study.

Procedures

The measurement schedule of RESCOM includes up to four measurement time-points (T1-T4) during the inpatient rehabilitation period (Figure 1). Following start of rehabilitation, newly injured patients are contacted for recruitment at about 4 weeks (T1) or at 12 weeks (T2) if the first six or more weeks following injury were spend on the ICU or in a general hospital for acute care. Subsequent assessments are planned at 24 weeks (T3) and at discharge to the community (T4). The T4 timepoint may precede and replace T2 and/or T3 in patients with a shorter length of inpatient rehabilitation stay. Temporal start and length of inpatient stay for rehabilitation varies with injury severity, general health status of patients and between countries and clinics. As such, between two and four measurement time-points are anticipated across patients, with those with more severe lesions and the longest length of stay providing more time points. In the four Swiss centers RESCOM is run as a "nested project" of the Swiss Spinal Cord Injury (SwiSCI) cohort study (www.swisci.ch).[20] The temporal schedule of data collection of RESCOM is aligned to that of SwiSCI and the relevant data for RESCOM will be extracted from the SwiSCI database additionally to RESCOM specific measurements and questionnaires.

Quality control

Each of the participating centres has one or two responsible study nurses. Before the start of recruitment, a study nurse meeting in the Swiss Paraplegic Centre Nottwil was performed to train all study nurses for the procedures and the assessments of the study. A study manual has been established to give an overview of the procedures and all assessed variables. A frequently asked question sheet is available in the study specific database (secuTrial®, iAS, Berlin, Germany) with all relevant questions the study nurses asked during data collection. For quality control of data assessment, regular central (database secuTrial®) and one local monitoring visit in each of the participating centers are performed. The coordinating study center supports one central study

coordinator who is responsible for central and local monitoring as well as for support of the local study nurses for questions concerning patient inclusion, data collection and entry into the database.

Parameters assessed

Primary outcome

The occurance of pneumonia is the primary outcome of RESCOM, observed continuously during the whole risk period of interest from time of injury until the end of inpatient rehabilitation. Medical records of inpatients are screened for diagnosis of pneumonia, including records from the acute care phase before admission to the rehabilitation center. Pneumonia is classified by type and cause, and the date of onset and duration of each event is recorded. Pneumonia is clinically diagnosed using the criteria described in the pneumonia flow diagram as endorsed by the Center for Disease Control and Prevention (CDC).[21] Mortality is defined as pneumonia-related, if pneumonia was clinically recorded as the initiating cause of events leading to death. Other causes of death are similarly classified.

Participant characteristics

All participant characteristics are obtained from medical records. Basic characteristics that are collected at T1 include gender, age, height, cause of SCI (traumatic or non-traumatic) and smoking history. Parameters that may temporally vary, including body weight, motor lesion level and American Spinal Injury Association Impairment Scale (AIS), medication, frequency of defecation as well as medical complications are assessed on all available measurement time-points. At T4, the actual smoking status and ICD-10 coded co-morbidities are recorded additionally.

Additional parameters

Additional parameters assessed at all measurement time-points, i.e. up to four times per participant (further details on these measurements and questionnaires are given below):

- Measurement of respiratory muscle strength and lung function
- ISCoS Pulmonary function data set[22]
- Quantiative questionnaire on physical exercise training
- Quantitative questionnaire on respiratory therapy and respiratory muscle training
- Bogenhausener Dysphagia score (BODS)
- ISCoS Quality of Life questionnaire [23]

- COVID-19 assessment form

Measurement of respiratory function

Measurement of respiratory function consists of respiratory muscle strength (maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max})) and lung function with forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), peak expiratory flow (PEF) and peak cough flow (PCF). All measurements are performed at the same day according to the ATS/ERS guidelines [24] in a sitting position either in the participant's own wheelchair or on a chair in participants that are able to walk. To derive a reliable estimate of the highest value for each parameter, each measurement is repeated until the three highest values of a given parameter are within a 20% range. The highest value of each parameter is retained for further analysis.[25]

Measurement of respiratory muscle strength and lung function have been harmonized across the 10 centers using identical equipment. PI_{max} and PE_{max} are measured using a hand-held respiratory pressure meter (Micro RPM, Micro Medical, Hoechberg, Germany). The PI_{max} measurement is derived from residual volume and PE_{max} from total lung capacity, against the occluded one-way valve of the respiratory pressure meter with the pressure maintained for at least one second. To derive the maximum pressure over a one second period, the patient is instructed to maintain in- and expiratory pressure for at least 1.5 seconds.[26] Abdominal binders are removed prior to any measurement of respiratory function.[27]

The FVC is the total volume of air the participant is able to exhale after a maximal inspiration. The FEV_1 is the total volume of air that has been exhaled at the end of the first second of maximal forced expiration. PEF is the maximum flow of air achieved during the maximum expiratory flow manoeuver. [28] During the PCF manoeuver the maximum flow of air is measured by having the participant cough as forcefully as possible through a peak flow meter. Participants breathe through a mouthpiece while wearing a nose clip. Across study centers, lung function parameters are measured accordingly, but using three different brands of portable spirometer, including Micro Loop® (Care Fusion, Basingstoke, UK; all Swiss, Dutch and German centers), EasyOne Spirometer® (Niche Medical, Melbourne, Australia; Australian center), Masterscreen PFT Pro® (Care Fusion, Hoechberg Germany; one Austrian center) and Vitalograph® (Ennis, Ireland; one Austrian center).

ISCoS Pulmonary function data set

The ISCoS Pulmonary function data set [22] consists of questions on pulmonary complications (asthma, chronic obstructive pulmonary disease, sleep apnea and others) before and after SCI, smoking history, current utilization of pulmonary assistance and lung function measurement.

Questionnaires on physical exercise and respiratory muscle training as well as on respiratory therapy

The questionnaires on individual respiratory muscle training, regular physical exercise and therapy are kept as simple as possible. Only quantitative or yes/no questions on physical activities performed during the last seven days are asked. Physical activity, duration of sport activities as well as number of physiotherapy sessions per week are recorded. Respiratory therapies such as mobilisation of secretions, manual blowing or air stacking and in-/exsufflation are assessed on a yes/no basis and if yes, whether with or without manual cough assistance. Respiratory muscle training is assessed separately for in- and expiratory muscle strength training as well as respiratory muscle endurance training (i.e. isocapnic hyperpnoea). In case of training, the name of the device, the number of training sessions per week, the number of repetitions per session as well as the resistance is noted.

Bogenhausener Dysphagia score (BODS)

Dysphagia is assessed using the Bogenhausener Dysphagia score (BODS), which consist of two scales, each with a score from 1 to 8, resulting in a sum-score of 2 to 16. The first scale quantifies swallowing of saliva and whether the patient has a tracheal cannula. For patients with tracheal cannula, the degree of blocking is quantified as fully, partly or mainly not blocked. The second scale quantifies problems with oral ingestion including four of the eight scores for parenteral nutrition. The BODS is assessed by a speech therapist or a physiotherapist, in close coordination with the RESCOM study nurse.

ISCoS quality of life questionnaire

Quality of Life (QoL) is evaluated using the ISCoS QoL questionnaire.[23] This measurement instrument accepts a multi-facetted concept and includes three questions that capture general QoL (overall well-being), rating of physical health, and satisfaction with psychological health.

COVID-19 assessment form

At the start of the COVID-19 pandemic (March 2020) we implemented an additional form into the study database and instructed all study nurses of each participating center to additionally fill in this form for the already included and future patients. Since COVID-19 infections are often leading to severe pneumonia and probably also death, we identified this as a potential confounder of our study results and therefore have to include this infection into our ananlysis. The COVID-19 form includes information on diagnosis, date of diagnosis, symptoms and death due to COVID-19.

Database secuTrial®

To enable secure capture and management of RESCOM data, the professional and web-browser based database system secuTrial® is used. SecuTrial® fulfills the minimal requirements for data storage and management indicated in the ICG-GCP guidelines and also supports the central monitoring of data collection across all participating centers. Database set-up, personal accounts with pre-defined roles for all study collaborators as well as support, data export and archiving is provided by a study-independent database manager from the study-center in Nottwil, Switzerland.

Methods of minimizing bias

Study participants receive an introduction for the study procedure by the local study nurse skilled in the management of persons with SCI and trained for all study specific tasks. A standardized study protocol was defined to minimize attrition bias.

The coding of the participants is conducted by the study nurses of each site in order to keep the data management and the biostatistician blinded (de-identified at source). The coding list remains with the study nurses of each site for the whole duration of the study and archiving period. Thus, coding is conducted without any influence of the principal investigator, the data manager or biostatistician. The study investigators strive for complete separation of the persons involved in the steps of enrolment and data collection from those involved in the data management and analysis.

All assessments are conducted and entered into the study database by the trained study nurse(s) of each participating center.

Patient and Public Involvement

No patients or public have been directly involved in the planning or conduct of this study. Study results will be disseminated to the scientific community through peer-reviewed journals and conference presentations, to the SCI community, other stakeholders and via social media, newsletters and engagement activities.

Statistics

Statistical analysis will involve basic descriptive statistics and multivariable regression analyses that take into account the longitudinal and multilevel structure of the data. A global overview of the multivariable data analysis plan for investigating the association between respiratory function and pneumonia is given in Figure 2. To evaluate variation in pneumonia risk, time-to-event analysis techniques (e.g., flexible parametric survival modeling) will be employed, taking date of injury as the starting point of the risk period. Regression models targeting causal inference will make use of time-updated information for all variables in accordance with the repeated measurement schedule of RESCOM, while controlling for between-person and between-center sources of variance using random and fixed effects. The exposure 'respiratory function' will be operationalized using parameters of respiratory muscle strength and parameters of lung function, as a latent construct within generalized latent variable modeling or as individual parameters in selected analysis as required.[29] Critical confounders that have been defined using evidence from the literature and expert opinion of RESCOM collaborators include age, lesion severity, time since injury (structurally captured in time-to-event modelling), artificial ventilation and medication. Models targeting prognosis of pneumonia during first rehabilitation will only include parameters of respiratory function that have been collected at baseline.[30] [31]

ETHICS AND DISSEMINATION

Full ethical approval for this project has been obtained by all local ethics committees of all participating centers. We certify that all applicable institutional and governmental regulations concerning the ethical use of data of human volunteers are followed during the course of this research.

Potential protocol modifications and amendments will be submitted to the ethical committees for approval. This project has been registered with ClinicalTrials.gov NCT02891096 and regular study updates are presented on Research Gate (https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury).

All participants give written or witnessed verbal consent if upper limb function is too impaired for a participant to sign, prior to entering the study.

The study results will be disseminated through publication in scientific journals, presentation at relevant conferences, directly to the participants and clinicians as well as on social media and in newsletters. The dissemination aims to provide clinicians with reliable prognostic factors to identify persons who are at heightened risk of pneumonia and thus, to effectively reduce pneumonia risk and pneumonia-related hospitalizations.

STRENGTH AND LIMITATIONS

RESCOM is the first prospective, international study that reports modifiable predictors of pneumonia from a representative sample of persons with SCI during inpatient rehabilitation. Its comprehensive evidence base facilitates the systematic evaluation of the discriminatory power of respiratory function parameters for pneumonia risk in high income countries.

The RESCOM study is effective in recruiting a representative sample of inpatients with a motor complete or incomplete SCI in Austria, Australia, Germany, The Netherlands and Switzerland. The anticipated minimal sample size of 500 should provide project sufficient statistical power to answer the key hypothesis that respiratory function, and PI_{max} in particular, is a strong prognostic parameter that quantifies clinical pneumonia risk in SCI. The longitudinal, international design of this project is considered a further strength; participants can be observed during the whole period of inpatient rehabilitation in different countries. Various factors like a central web-based database, a study nurse meeting, a comprehensive study manual and regular monitoring were implemented to ensure the standardization of the measurements and data and thus to keep quality of the project in the 10 centers as high as possible.

For data collection we used the International SCI Core Data Set, [32 33] the International SCI QoL Basic Data Set [23] and the International SCI Pulmonary Function Data Set [22] which are developed to provide global data standards for SCI clinical research. The advantage of using these standardized data sets is to increase the data quality and to facilitate data sharing.

Potential limitations include the observational nature of the project which limits causal inference even within a prospective study design. Although the RESCOM sample reflects the composition of the source population quite well, we cannot exclude potential selection bias and therefore, the results of

the RESCOM project may not be transferable to all persons with SCI. There is a risk that the study inclusion and exclusion criteria may miss those patients with a potential high risk of pneumonia because those with more severe lesions or more complications may not consent to participate in an observational study that may not directly increase their outcome. Similalry, patients with a very long stay in the intensive care unit (e.g. due to polytrauma) or a very late admission to the rehabilitation unit, may miss T2 and therefore no more qualify for study participation. Those patients with 24h of mechanical ventilation are excluded since respiratory function cannot be measured and also those with other languages than used in our study centers are excluded. Another limitation of this project is that we do not have a follow-up period after the participants complete inpatient rehabilitation.

In summary, using discriminatory parameters of respiratory function, clinicians may identify persons with SCI who are at heightened risk of developing pneumonia during inpatient rehabilitation. Thus, interventions can be targeted at these persons to reduce pneumonia risk. The RESCOM study is well-positioned to determine prognostic parameters of respiratory function for pneumonia risk in SCI.

Acknowledgements

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Collaborators

This study offers options of scientific collaborations.

Author Contributions

GM is the principal investigator of the RESCOM project. AMR and GM designed the study. MWGB provided statistical and methodological support. DJB, KP, DG, SH, MTEH, BH, MHG, XJ, MS and RW provided clinical support and/or are responsible for data collection in their respective clinics. AMR, MWGB and GM drafted the work and DJB, KP, DG, SH, MTEH, BH, MHG, XJ, MS and RW revised it critically for important intellectual content. AMR was responsible for the monitoring-visits. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data Availability Statement

After completion of data collection and analysis, all relevant data and stimates of ths study will be deposited on Dryad.

Funding

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Competing Interests

The authors declare no conflict of interest.

Patient consent

Obtained.

Registration

Further details about the study can be found under ClinicalTrials.gov NCT02891096 and regular study updates are presented on Research Gate (https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury).

Ethics approval: Approved by all local ethics committees of all participating centers, namely: for Switzerland: ethics committee north-west and central Switzerland (EKNZ) for the two Swiss Centres SPZ Nottwil and REHAB Basel, ethics committee Zurich, Switzerland for the Balgrist, Zurich and Ethics Committee Vaud, Switzerland for the CRR Sion (Nr. 2016-01065 – one multi-centric application for all Swiss centres). In Germany from the 'Ethikkommission der Ärztekammer Hamburg' (Nr. PV 5502); for Austria from the 'Ethikkommission der Medizinischen Universität Innsbruck' (Nr. AN-2016-0176) and the 'Ethikkommission für die Krankenanstalten der AUVA' (Nr. 6/2016). In the Netherlands from the medical ethics committee of the Erasmus Medical Centre Rotterdam (Nr. MEC-2016-594) and for Autralia from the Austin Health Human Research Ethics Committee (Nr. LNR/16/Austin/422).

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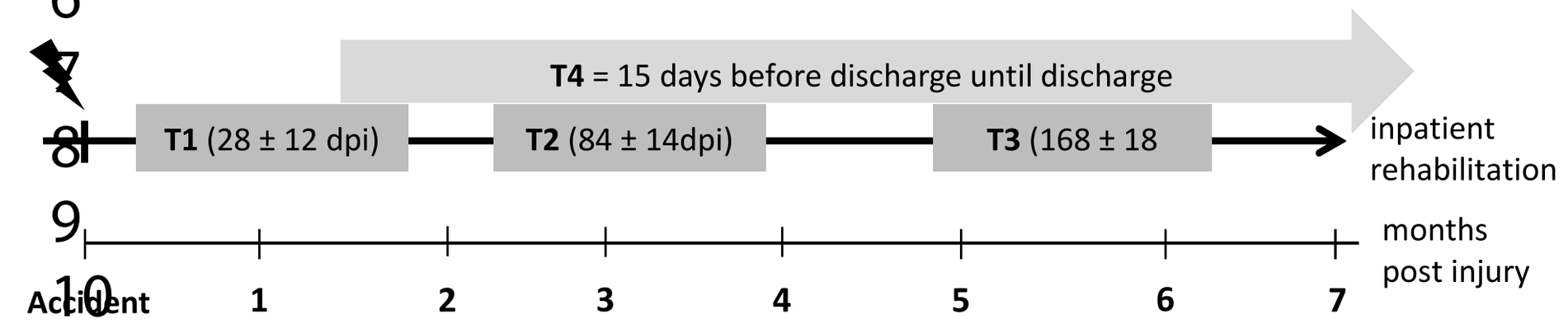
FIGURE LEGENDS

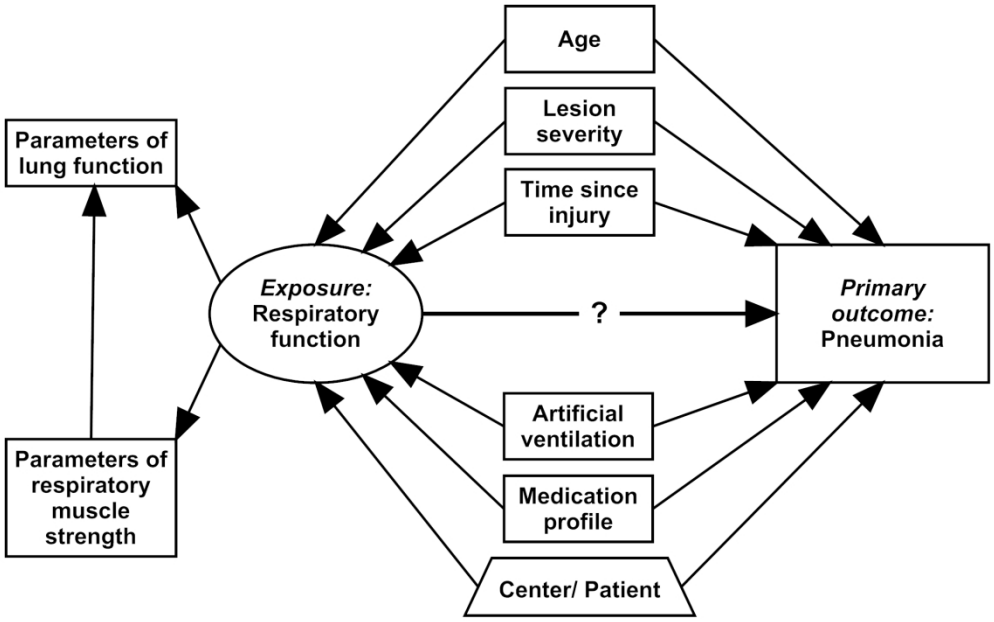
Figure 1

Time frames for measurements (T1 toT4) during inpatient rehabilitation. T1-T3 time-windows with days post injury (dpi) are shown by blue bars and T4 by the green bar above.

Figure 2

Global scheme of the planned data analysis investigating the dynamic association between respiratory function and pneumonia. In regression modelling all variables will be time-updated in accordance with the repeated measurement schedule of RESCOM and controlling for between-person and between-center sources of variance. Respiratory function is operationalized using parameters of respiratory muscle strength and parameters of lung function.





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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6/7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6/7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11/Fig.2
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a. since this is a protocol paper
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n.a. since this is a protocol paper
		(b) Indicate number of participants with missing data for each variable of interest	

		(c) Summarise follow-up time (eg, average and total amount)	n.a. since this is a protocol paper
Outcome data	15*	Report numbers of outcome events or summary measures over time	n.a. since this is a protocol paper
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a. since this is a protocol paper
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a. since this is a protocol paper
Discussion			
Key results	18	Summarise key results with reference to study objectives	n.a. since this is a protocol paper
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12/13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n.a. since this is a protocol paper
Generalisability	21	Discuss the generalisability (external validity) of the study results	12/13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.