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# 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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33 **Running title**

34 Protocol of the RESCOM study

35

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3 **47 ABSTRACT**  
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8 **Introduction:** Pneumonia is one of the leading complications and causes of death after a spinal cord  
9 injury (SCI). After a cervical or thoracic lesion, impairment of the respiratory muscles decreases  
10 respiratory function, which increases the risk of respiratory complications. Pneumonia substantially  
11 reduce patient's quality of life, prolong inpatient rehabilitation time, increase health care costs, or at  
12 worse, lead to early death. Respiratory function and coughing can be improved through various  
13 interventions after SCI, but the available evidence as to which aspect of respiratory care should be  
14 optimized is inconclusive. Further, ability of respiratory function parameters to predict pneumonia risk  
15 is insufficiently established. This paper details the protocol for a large-scale, multicenter research  
16 project that aims to evaluate the ability of parameters of respiratory function to predict and understand  
17 variation in inpatient risk of pneumonia in SCI.  
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19

20 **Methods and analysis:** RESCOM, a prospective cohort study, began recruitment in October 2016  
21 across 10 SCI rehabilitation centers from Australia, Austria, Germany, the Netherlands and  
22 Switzerland. In-patients with acute SCI, with complete or incomplete cervical or thoracic lesions, 18  
23 years or older and not dependent on 24-hour mechanical ventilation are eligible for inclusion. The  
24 target sample size is 500 participants. The primary outcome is an occurrence of pneumonia; secondary  
25 outcomes include pneumonia-related mortality and quality of life. We will use the longitudinal data for  
26 prognostic models on inpatient pneumonia risk-factors.  
27  
28

29 **Ethics and dissemination:** The study has been reviewed and approved by all local ethics committees  
30 of all participating centers. Study results will be disseminated to the scientific community through peer-  
31 reviewed journals and conference presentations, to the SCI community, other stakeholders and via  
32 social media, newsletters and engagement activities.  
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35 **Registration details:** ClinicalTrials.gov NCT02891096  
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52 **Keywords:** 1. spinal cord injury 2. respiratory muscle strength 3. pneumonia  
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3 73 **ARTICLE SUMMARY**  
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7 75 **Strengths and limitations of this study**  
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11 77 • RESCOM (for RESpiratory COMplications) is the first multinational study to prospectively  
12  
13 78 evaluate predictors of pneumonia from a representative sample of persons with spinal cord  
14  
15 79 injury (SCI) receiving inpatient rehabilitation in a high-income setting.  
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19 81 • The RESCOM cohort will enroll 500 persons with SCI to develop generalizable prognostic  
20  
21 82 models as well as to validate causal risk factors, specifically impaired respiratory function, of  
22  
23 83 pneumonia risk.  
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26  
27 85 • Because respiratory function following SCI may be improved through respiratory muscle  
28  
29 86 training, study results may inform and improve current clinical practice and patient  
30  
31 87 management through the better targeting of interventions.  
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35 89 • Generalizability of the study with respect to pneumonia risk is limited to patients with less than  
36  
37 90 24 hours of mechanical ventilation because respiratory function cannot be measured using  
38  
39 91 standard techniques in those who are intubated, as well as patients with a poor general health  
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41 92 status or facing other severe secondary morbidity may not consent to study participation or  
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43 93 may not participate in all of the measurements over time.  
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## 95 INTRODUCTION

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

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

110  
111 Impairment of respiratory function represents the most promising target for clinically relevant research  
112 on pneumonia in SCI, as these measures are directly linked to the neurological impairment and  
113 appear to be modifiable through targeted respiratory training.<sup>9-11</sup> Respiratory muscles below the level  
114 of injury may become paralyzed or impaired<sup>12</sup> and respiratory function is compromised with higher  
115 levels of injury causing greater impairment.<sup>9 13</sup> Cough impairment is also considered critically  
116 important, as insufficient removal of airway secretion may result in the development of mucus plugging  
117 and complications such as atelectasis or pneumonia.<sup>14 15</sup> Effective coughing comprises an inspiration,  
118 compression and expulsion phase. Cough impairment following SCI may affect each phase due to the  
119 weakening of inspiratory and expiratory muscle function, which may decrease the maximum volume of  
120 expelled air by restricting both the maximum inspiratory volume prior to contraction as well as a  
121 reduction in the amount able to be expelled.<sup>14 16</sup> The limited evidence in SCI suggests that inspiratory  
122 (using maximal inspiratory muscle pressure;  $PI_{max}$ ) rather than expiratory function (maximal expiratory  
123 muscle pressure;  $PE_{max}$ ) is the prime determinant of cough capacity (peak flow), particularly in patients  
124 with a motor-complete cervical SCI.<sup>17</sup> Postma et al. found that impaired pulmonary function may



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3 125 increase respiratory infections at one year after SCI, but their study did incorporate respiratory muscle  
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5 126 strengthening and respiratory complications were incompletely assessed.<sup>7</sup>  
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9 128 To the best of our knowledge, there is currently no comprehensive database available for the further  
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11 129 development of generalizable prognostic models, nor to improve causal inference of pneumonia risk in  
12  
13 130 light of impairment in respiratory function. The multicenter and multinational cohort study RESCOM  
14  
15 131 aims to establish such an evidence base in SCI. We believe RESCOM will thereby improve clinical  
16  
17 132 practice through better targeting of interventions during the inpatient setting in high-income countries.  
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19 133

## 20 134 **METHODS AND ANALYSES**

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### 23 24 136 **Design and setting**

25  
26 137 RESCOM is a prospective international, multi-center cohort study in high income countries. Data  
27  
28 138 collection commenced in October 2016 across 10 specialized rehabilitation centers for SCI from  
29  
30 139 Austria (2 centers), Australia (1 center), Germany (1 center), The Netherlands (2 centers) and  
31  
32 140 Switzerland (4 centers) and is still ongoing.  
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34 141

### 35 36 142 **Study population**

37  
38 143 Newly injured persons who are aged 18 years or older, admitted for inpatient rehabilitation in the  
39  
40 144 participating centers, with complete or incomplete lesions (grades A-D on the American Spinal Injury  
41  
42 145 Association Impairment Scale (AIS)<sup>18</sup> and cervical or thoracic lesion levels (right and left motor level  
43  
44 146 between C1- T12). Persons with severe pre-existing scoliosis, progressive neurological diseases, 24h  
45  
46 147 mechanical ventilation dependency until more than 3 months post injury or severe mental disorders  
47  
48 148 are excluded.  
49  
50 149

### 51 150 **Sample Size**

52  
53 151 A retrospective study in one of the Swiss participating centers indicated good discriminatory power for  
54  
55 152 key dimensions of respiratory muscle strength based on a total number of 110 episodes of  
56  
57 153 pneumonia.<sup>19</sup> To meet the study purposes for RESCOM we estimated the cumulative number of  
58  
59 154 pneumonia events at 100. The minimal adequate sample size to observe 100 pneumonia cases was  
60  
155 calculated by applying RESCOM inclusion criteria to the inception cohort of the Swiss Spinal Cord

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3 156 Injury (SwiSCI) study. A minimal sample size of 500 was required to observe a pneumonia prevalence  
4  
5 157 rate of 20% in the SwiSCI cohort.<sup>20</sup>  
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7 158

### 8 9 159 **Procedures**

10 160 The measurement schedule of RESCOM includes up to four measurement time-points (T1-T4) during  
11  
12 161 the inpatient rehabilitation period (Figure 1). Following start of rehabilitation, newly injured patients are  
13  
14 162 contacted for recruitment at about 4 weeks (T1) or at 12 weeks (T2) if the first six or more weeks  
15  
16 163 following injury were spent on the ICU or in a general hospital for acute care. Subsequent  
17  
18 164 assessments are planned at 24 weeks (T3) and at discharge to the community (T4). The T4 timepoint  
19  
20 165 may precede and replace T2 and/or T3 in patients with a shorter length of inpatient rehabilitation stay.  
21  
22 166 Temporal start and length of inpatient stay for rehabilitation varies with injury severity, general health  
23  
24 167 status of patients and between countries and clinics. As such, between two and four measurement  
25  
26 168 time-points are anticipated across patients, with those with more severe lesions and the longest length  
27  
28 169 of stay providing more time points. In the four Swiss centers RESCOM is run as a “nested project” of  
29  
30 170 the Swiss Spinal Cord Injury (SwiSCI) cohort study ([www.swisci.ch](http://www.swisci.ch)).<sup>20</sup> The temporal schedule of data  
31  
32 171 collection of RESCOM is aligned to that of SwiSCI and the relevant data for RESCOM will be  
33  
34 172 extracted from the SwiSCI database additionally to RESCOM specific measurements and  
35  
36 173 questionnaires.

37 174

### 39 175 **Quality control**

41 176 *Each of the participating centres has one or two responsible study nurses.* Before the start of recruitment, a study nurse  
42  
43 177 meeting in the Swiss Paraplegic Centre Nottwil was performed to train all study nurses for the  
44  
45 178 procedures and the assessments of the study. A study manual has been established to give an  
46  
47 179 overview of the procedures and all assessed variables. A frequently asked question sheet is available  
48  
49 180 in the study specific database (secuTrial®, iAS, Berlin, Germany) with all relevant questions the study  
50  
51 181 nurses asked during data collection. For quality control of data assessment, regular central (database  
52  
53 182 secuTrial®) and one local monitoring visit in each of the participating centers are performed. The  
54  
55 183 coordinating study center supports one central study coordinator who is responsible for central and  
56  
57 184 local monitoring as well as for support of the local study nurses for questions concerning patient  
58  
59 185 inclusion, data collection and entry into the database.

60 186

## 187 **Parameters assessed**

188 Primary outcome

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

197

### 198 *Participant characteristics*

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

205

### 206 *Additional parameters*

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

- 208 - Measurement of respiratory muscle strength and lung function
- 209 - ISCoS Pulmonary function data set <sup>22</sup>
- 210 - Quantitative questionnaire on physical exercise training
- 211 - Quantitative questionnaire on respiratory therapy and respiratory muscle training
- 212 - Bogenhausener Dysphagia score (BODS)
- 213 - ISCoS Quality of Life questionnaire <sup>23</sup>

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### 215 *Measurement of respiratory function*

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

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3 218 (FVC), forced expiratory volume in 1s (FEV<sub>1</sub>), peak expiratory flow (PEF) and peak cough flow (PCF).  
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5 219 All measurements are performed at the same day according to the ATS/ERS guidelines<sup>24</sup> in a sitting  
6  
7 220 position either in the participant's own wheelchair or on a chair in participants that are able to walk. To  
8  
9 221 derive a reliable estimate of the highest value for each parameter, each measurement is repeated until  
10  
11 222 the three highest values of a given parameter are within a 20% range. The highest value of each  
12  
13 223 parameter is retained for further analysis.<sup>25</sup>

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15 224

16 225 Measurement of respiratory muscle strength and lung function have been harmonized across the 10  
17  
18 226 centers using identical equipment. P<sub>I</sub><sub>max</sub> and P<sub>E</sub><sub>max</sub> are measured using a hand-held respiratory  
19  
20 227 pressure meter (Micro RPM, Micro Medical, Hoechberg, Germany). The P<sub>I</sub><sub>max</sub> measurement is derived  
21  
22 228 from residual volume and P<sub>E</sub><sub>max</sub> from total lung capacity, against the occluded one-way valve of the  
23  
24 229 respiratory pressure meter with the pressure maintained for at least one second. To derive the  
25  
26 230 maximum pressure over a one second period, the patient is instructed to maintain in- and expiratory  
27  
28 231 pressure for at least 1.5 seconds.<sup>26</sup> Abdominal binders are removed prior to any measurement of  
29  
30 232 respiratory function.<sup>27</sup>

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33  
34 234 The FVC is the total volume of air the participant is able to exhale after a maximal inspiration. The  
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36 235 FEV<sub>1</sub> is the total volume of air that has been exhaled at the end of the first second of maximal forced  
37  
38 236 expiration. PEF is the maximum flow of air achieved during the maximum expiratory flow manoeuvre.  
39  
40 237<sup>28</sup> During the PCF manoeuvre the maximum flow of air is measured by having the participant cough as  
41  
42 238 forcefully as possible through a peak flow meter. Participants breathe through a mouthpiece while  
43  
44 239 wearing a nose clip. Across study centers, lung function parameters are measured accordingly, but  
45  
46 240 using three different brands of portable spirometer, including Micro Loop<sup>®</sup> (Care Fusion, Basingstoke,  
47  
48 241 UK; all Swiss, Dutch and German centers), EasyOne Spirometer<sup>®</sup> (Niche Medical, Melbourne,  
49  
50 242 Australia; Australian center), Masterscreen PFT Pro<sup>®</sup> (Care Fusion, Hoechberg Germany; one  
51  
52 243 Austrian center) and Vitalograph<sup>®</sup> (Ennis, Ireland; one Austrian center).

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#### 55 245 *ISCoS Pulmonary function data set*

56 246 The ISCoS Pulmonary function data set<sup>22</sup> consists of questions on pulmonary complications (asthma,  
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58 247 chronic obstructive pulmonary disease, sleep apnea and others) before and after SCI, smoking  
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60 248 history, current utilization of pulmonary assistance and lung function measurement.

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5 250 *Questionnaires on physical exercise and respiratory muscle training as well as on respiratory therapy*  
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7 251 The questionnaires on individual respiratory muscle training, regular physical exercise and therapy are  
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9 252 kept as simple as possible. Only quantitative or yes/no questions on physical activities performed  
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11 253 during the last seven days are asked. Physical activity, duration of sport activities as well as number of  
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13 254 physiotherapy sessions per week are recorded. Respiratory therapies such as mobilisation of  
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15 255 secretion, manual blowing or air stacking and in-/exsufflation are assessed on a yes/no basis and if  
16  
17 256 yes, whether with or without manual cough assistance. Respiratory muscle training is assessed  
18  
19 257 separately for in- and expiratory muscle strength training as well as respiratory muscle endurance  
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21 258 training (i.e. isocapnic hyperpnoea). In case of training, the name of the device, the number of training  
22  
23 259 sessions per week, the number of repetitions per session as well as the resistance is noted.

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26 261 *Bogenhausener Dysphagia score (BODS)*  
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28 262 Dysphagia is assessed using the Bogenhausener Dysphagia score (BODS), which consist of two  
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30 263 scales, each with a score from 1 to 8, resulting in a sum-score of 2 to 16. The first scale quantifies  
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32 264 swallowing of saliva and whether the patient has a tracheal cannula. For patients with tracheal  
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34 265 cannula, the degree of blocking is quantified as fully, partly or mainly not blocked. The second scale  
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36 266 quantifies problems with oral ingestion including four of the eight scores for parenteral nutrition. The  
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38 267 BODS is assessed by a speech therapist or a physiotherapist, in close coordination with the RESCOM  
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40 268 study nurse.

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43 270 ISCoS quality of life questionnaire  
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45 271 Quality of Life (QoL) is evaluated using the ISCoS QoL questionnaire.<sup>23</sup> This measurement instrument  
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47 272 accepts a multi-facetted concept and includes three questions that capture general QoL (overall well-  
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49 273 being), rating of physical health, and satisfaction with psychological health.

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53 275 **Database secuTrial®**  
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55 276 To enable secure capture and management of RESCOM data, the professional and web-browser  
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57 277 based database system secuTrial® is used. SecuTrial® fulfills the minimal requirements for data  
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59 278 storage and management indicated in the ICG-GCP guidelines and also supports the central  
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279 monitoring of data collection across all participating centers. Database set-up, personal accounts with

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3 280 pre-defined roles for all study collaborators as well as support, data export and archiving is provided  
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5 281 by a study-independent database manager from the study-center in Nottwil, Switzerland.

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### 8 283 **Methods of minimizing bias**

9  
10 284 Study participants receive an introduction for the study procedure by the local study nurse skilled in  
11  
12 285 the management of persons with SCI and trained for all study specific tasks. A standardized study  
13  
14 286 protocol was defined to minimize attrition bias.

15  
16 287 The coding of the participants is conducted by the study nurses of each site in order to keep the data  
17  
18 288 management and the biostatistician blinded (de-identified at source). The coding list remains with the  
19  
20 289 study nurses of each site for the whole duration of the study and archiving period. Thus, coding is  
21  
22 290 conducted without any influence of the principal investigator, the data manager or biostatistician. The  
23  
24 291 study investigators strive for complete separation of the persons involved in the steps of enrolment  
25  
26 292 and data collection from those involved in the data management and analysis.

27  
28 293 All assessments are conducted and entered into the study database by the trained study nurse(s) of  
29  
30 294 each participating center.

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### 33 296 **Statistics**

34  
35 297 Statistical analysis will involve basic descriptive statistics and multivariable regression analyses that  
36  
37 298 take into account the longitudinal and multilevel structure of the data. A global overview of the  
38  
39 299 multivariable data analysis plan for investigating the association between respiratory function and  
40  
41 300 pneumonia is given in Figure 2. To evaluate variation in pneumonia risk, time-to-event analysis  
42  
43 301 techniques (e.g., flexible parametric survival modeling) will be employed, taking date of injury as the  
44  
45 302 starting point of the risk period. Regression models targeting causal inference will make use of time-  
46  
47 303 updated information for all variables in accordance with the repeated measurement schedule of  
48  
49 304 RESCOM, while controlling for between-person and between-center sources of variance using random  
50  
51 305 and fixed effects. The exposure 'respiratory function' will be operationalized using parameters of  
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53 306 respiratory muscle strength and parameters of lung function, as a latent construct within generalized  
54  
55 307 latent variable modeling or as individual parameters in selected analysis as required.<sup>29</sup> Critical  
56  
57 308 confounders that have been defined using evidence from the literature and expert opinion of RESCOM  
58  
59 309 collaborators include age, lesion severity, time since injury (structurally captured in time-to-event  
60  
310 modelling), artificial ventilation and medication. Models targeting prognosis of pneumonia during first

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3 311 rehabilitation will only include parameters of respiratory function that have been collected at baseline.<sup>30</sup>

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9 314 **ETHICS AND DISSEMINATION**

10 315 Full ethical approval for this project has been obtained by all local ethics committees of all participating  
11 316 centers. We certify that all applicable institutional and governmental regulations concerning the ethical  
12 317 use of data of human volunteers are followed during the course of this research.

13 318 Potential protocol modifications and amendments will be submitted to the ethical committees for  
14 319 approval. This project has been registered with ClinicalTrials.gov NCT02891096 and regular study  
15 320 updates are presented on Research Gate ([https://www.researchgate.net/project/RESCOM-  
16 321 RESpiratory-COMplications-after-Spinal-Cord-Injury](https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury)).

17 322 All participants give written or witnessed verbal consent if upper limb function is too impaired for a  
18 323 participant to sign, prior to entering the study.

19 324 The study results will be disseminated through publication in scientific journals, presentation at  
20 325 relevant conferences, directly to the participants and clinicians as well as on social media and in  
21 326 newsletters. The dissemination aims to provide clinicians with reliable prognostic factors to identify  
22 327 persons who are at heightened risk of pneumonia and thus, to effectively reduce pneumonia risk and  
23 328 pneumonia-related hospitalizations.

24 329

25 330 **STRENGTH AND LIMITATIONS**

26 331 RESCOM is the first prospective, international study that reports modifiable predictors of pneumonia  
27 332 from a representative sample of persons with SCI during inpatient rehabilitation. Its comprehensive  
28 333 evidence base facilitates the systematic evaluation of the discriminatory power of respiratory function  
29 334 parameters for pneumonia risk in high income countries.

30 335 The RESCOM study is effective in recruiting a representative sample of inpatients with a motor  
31 336 complete or incomplete SCI in Austria, Australia, Germany, The Netherlands and Switzerland. The  
32 337 anticipated minimal sample size of 500 should provide project sufficient statistical power to answer the  
33 338 key hypothesis that respiratory function, and  $PI_{max}$  in particular, is a strong prognostic parameter that  
34 339 quantifies clinical pneumonia risk in SCI. The longitudinal, international design of this project is  
35 340 considered a further strength; participants can be observed during the whole period of inpatient  
36 341 rehabilitation in different countries. Various factors like a central web-based database, a study nurse

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3 342 meeting, a comprehensive study manual and regular monitoring were implemented to ensure the  
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5 343 standardization of the measurements and data and thus to keep quality of the project in the 10 centers  
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7 344 as high as possible.  
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9 345  
10 346 For data collection we used the International SCI Core Data Set,<sup>32 33</sup> the International SCI QoL Basic  
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12 347 Data Set<sup>23</sup> and the International SCI Pulmonary Function Data Set<sup>22</sup> which are developed to provide  
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14 348 global data standards for SCI clinical research. The advantage of using these standardized data sets  
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16 349 is to increase the data quality and to facilitate data sharing.  
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18 350 Potential limitations include the observational nature of the project which limits causal inference even  
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20 351 within a prospective study design. Although the RESCOM sample reflects the composition of the  
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22 352 source population quite well, we cannot exclude potential selection bias and therefore, the results of  
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24 353 the RESCOM project may not be transferable to all persons with SCI. There is a risk that the study  
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26 354 inclusion and exclusion criteria may miss those patients with a potential high risk of pneumonia  
27  
28 355 because those with more severe lesions or more complications may not consent to participate in an  
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30 356 observational study that may not directly increase their outcome. Similarly, patients with a very long  
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32 357 stay in the intensive care unit or a very late admission to the rehabilitation unit, may miss T2 and  
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34 358 therefore no more qualify for study participation. Those patients with 24h of mechanical ventilation are  
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36 359 excluded since respiratory function cannot be measured and also those with other languages than  
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38 360 used in our study centers are excluded. Another limitation of this project is that we do not have a  
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40 361 follow-up period after the participants complete inpatient rehabilitation.  
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42 362  
43 363 In summary, using discriminatory parameters of respiratory function, clinicians may identify persons  
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45 364 with SCI who are at heightened risk of developing pneumonia during inpatient rehabilitation. Thus,  
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47 365 interventions can be targeted at these persons to reduce pneumonia risk. The RESCOM study is well-  
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49 366 positioned to determine prognostic parameters of respiratory function for pneumonia risk in SCI.  
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6  
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8  
9 370 Wings for Life (WFL-CH-014/16) and the Swiss Paraplegic Foundation for the SwiSCI nested project  
10  
11 371 start-up grant.

12 372  
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14 373 **Collaborators**

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16 374 This study offers options of scientific collaborations.  
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20 376 **Author Contributions**

21  
22 377 GM is the principal investigator of the RESCOM project. AMR and GM designed the study and AMR,  
23  
24 378 MWGB and GM wrote a first draft of this manuscript. AMR is responsible for the monitoring-visits. All  
25  
26 379 authors worked on, reviewed and approved the final version of the manuscript.  
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30 381 **Data Availability Statement**

31  
32 382 After completion of data collection and analysis, all relevant data and estimates of this study will be  
33  
34 383 deposited on Dryad.  
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36 384

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38  
39 386 This project is supported by Wings for Life, a spinal cord research foundation (Salzburg, Austria), grant  
40  
41 387 number WFL-CH-014/16. Start-up costs for the participating Swiss Centres were covered by the  
42  
43 388 SwiSCI nested project start-up grant of the Swiss Paraplegic Foundation.  
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47 390 **Competing Interests**

48  
49 391 The authors declare no conflict of interest.  
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53 393 **Patient consent**

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55 394 Obtained.  
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58 396 **Registration**  
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3 397 Further details about the study can be found under ClinicalTrials.gov NCT02891096 and regular study  
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5 398 updates are presented on Research Gate ([https://www.researchgate.net/project/RESCOM-](https://www.researchgate.net/project/RESCOM-REspiratory-COMplications-after-Spinal-Cord-Injury)  
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7 399 [REspiratory-COMplications-after-Spinal-Cord-Injury](https://www.researchgate.net/project/RESCOM-REspiratory-COMplications-after-Spinal-Cord-Injury)).

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11 401 **Ethics approval:** Approved by all local ethics committees of all participating centers.  
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For peer review only

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3 502 **FIGURE LEGENDS**  
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7 504 **Figure 1**

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9 505 Time frames for measurements (T1 to T4) during inpatient rehabilitation. T1-T3 time-windows with days  
10 506 post injury (dpi) are shown by blue bars and T4 by the green bar above.  
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16 509 **Figure 2**

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18 510 Global scheme of the planned data analysis investigating the dynamic association between respiratory  
19 511 function and pneumonia. In regression modelling all variables will be time-updated in accordance with  
20 512 the repeated measurement schedule of RESCOM and controlling for between-person and between-  
21 513 center sources of variance. Respiratory function is operationalized using parameters of respiratory  
22 514 muscle strength and parameters of lung function.  
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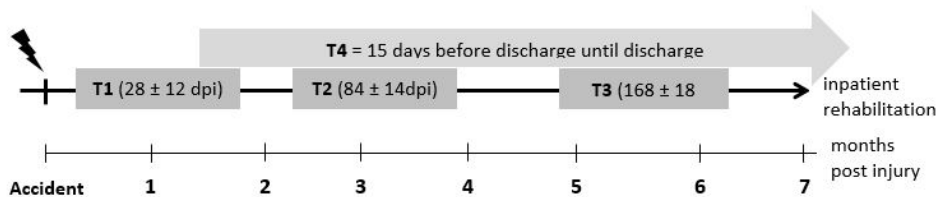


Figure 1  
 Time frames for measurements (T1 toT4) during inpatient rehabilitation. T1-T3 time-windows with days post injury (dpi) are shown by blue bars and T4 by the green bar above.

207x55mm (96 x 96 DPI)

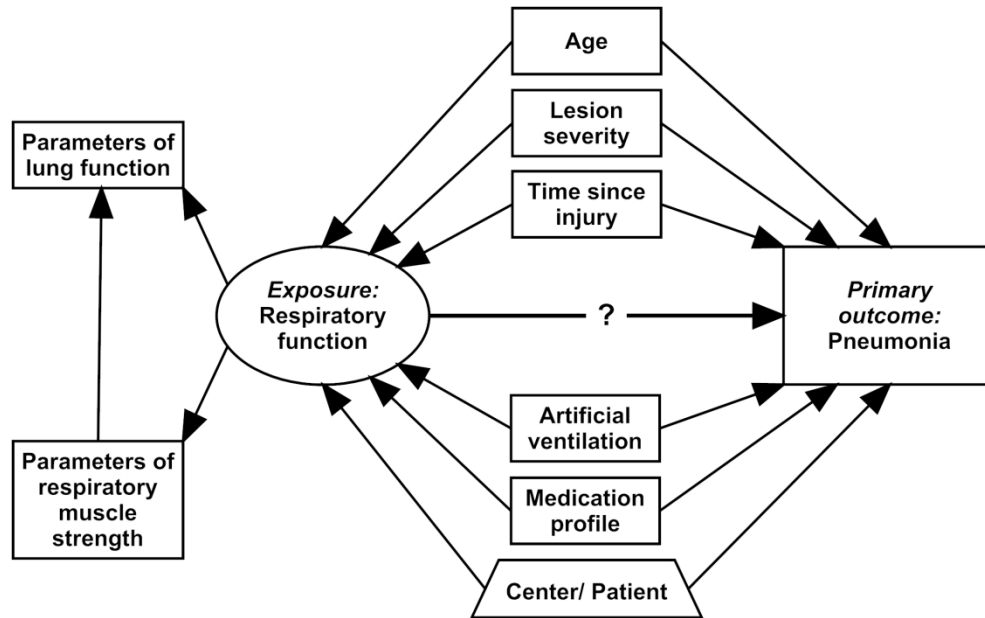


Figure 2

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.

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract  (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1  3
<b>Introduction</b>			
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
<b>Methods</b>			
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  (b) For matched studies, give matching criteria and number of exposed and unexposed	6/7  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  (b) Describe any methods used to examine subgroups and interactions  (c) Explain how missing data were addressed  (d) If applicable, explain how loss to follow-up was addressed  (e) Describe any sensitivity analyses	11  11/Fig.2 n.a. n.a. n.a.
<b>Results</b>			
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  (b) Give reasons for non-participation at each stage  (c) Consider use of a flow diagram	n.a. since this is a protocol paper
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  (b) Indicate number of participants with missing data for each variable of interest	n.a. since this is a protocol paper



		(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
<b>Discussion</b>			
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
<b>Other information</b>			
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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038204.R1
Article Type:	Protocol
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Complete List of Authors:	Raab, Anja; Swiss Paraplegic Centre, Clinical Trial Unit Brinkhof, Martin; Swiss Paraplegic Research, Berlowitz, David; Institute for Breathing and Sleep, Respiratory and Sleep Medicine; University of Melbourne, Department of Physiotherapy Postma, Karin; University Medical Center Rotterdam, Rijndam Rehabilitation and Erasmus MC Gobets, David; Heliomare Rehabilitation Center Hirschfeld, Sven; BG-Trauma Hospital Hopman, Maria; Radboud University Medical Center Huber, Burkhardt; AUVA Rehabilitation Center Haering Hund-Georgiadis, Margret; REHAB Basel Jordan, Xavier; Clinique romande de readaptation Schubert, Martin; University Hospital Balgrist Wildburger, Renate; AUVA Rehabilitation Clinic Tobelbad Mueller, Gabi; Swiss Paraplegic Centre, Clinical Trial Unit
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Rehabilitation medicine
Keywords:	Respiratory infections < THORACIC MEDICINE, REHABILITATION MEDICINE, EPIDEMIOLOGY

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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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30 <sup>13</sup>. Rehabilitation Clinic Tobelbad, Austria

31 ‡ equal contribution

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33 **Running title**

34 Protocol of the RESCOM study

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3 **47 ABSTRACT**  
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49 **Introduction:** Pneumonia is one of the leading complications and causes of death after a spinal cord  
50 injury (SCI). After a cervical or thoracic lesion, impairment of the respiratory muscles decreases  
51 respiratory function, which increases the risk of respiratory complications. Pneumonia substantially  
52 reduces patient's quality of life, prolong inpatient rehabilitation time, increase health care costs, or at  
53 worse, lead to early death. Respiratory function and coughing can be improved through various  
54 interventions after SCI, but the available evidence as to which aspect of respiratory care should be  
55 optimized is inconclusive. Further, ability of respiratory function parameters to predict pneumonia risk  
56 is insufficiently established. This paper details the protocol for a large-scale, multicenter research  
57 project that aims to evaluate the ability of parameters of respiratory function to predict and understand  
58 variation in inpatient risk of pneumonia in SCI.

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

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

71 **Registration details:** ClinicalTrials.gov NCT02891096  
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**Keywords:** 1. spinal cord injury 2. respiratory muscle strength 3. pneumonia  
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3 74 **ARTICLE SUMMARY**  
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7 76 **Strengths and limitations of this study**  
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- 11 78 • RESCOM (for RESpiratory COMplications) is the first multinational study to prospectively  
12 evaluate predictors of pneumonia from a representative sample of persons with spinal cord  
13 79 injury (SCI) receiving inpatient rehabilitation in a high-income setting.  
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15 80  
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17 81  
18  
19 82 • The RESCOM cohort will enroll 500 persons with SCI to develop generalizable prognostic  
20 models as well as to validate causal risk factors, specifically impaired respiratory function, of  
21 83 pneumonia risk.  
22  
23 84  
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25 85  
26 86 • Because respiratory function following SCI may be improved through respiratory muscle  
27 87 training, study results may inform and improve current clinical practice and patient  
28 management through the better targeting of interventions.  
29 88  
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31 89  
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33  
34 90 • Generalizability of the study with respect to pneumonia risk is limited to patients with less than  
35 91 24 hours of mechanical ventilation within the first three months post injury, because  
36 respiratory function cannot be measured using standard techniques in those who are  
37 92 intubated.  
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42 95 • This study will provide insight whether the improvement of respiratory muscle strength and  
43 respiratory function represent promising targets for intervention to reduce pneumonia risk  
44 96 following spinal cord injury.  
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## 99 INTRODUCTION

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

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

116  
117 Impairment of respiratory function represents the most promising target for clinically relevant research  
118 on pneumonia in SCI, as these measures are directly linked to the neurological impairment and  
119 appear to be modifiable through targeted respiratory training.<sup>10-12</sup> Respiratory muscles below the level  
120 of injury may become paralyzed or impaired<sup>13</sup> and respiratory function is compromised with higher  
121 levels of injury causing greater impairment.<sup>10 14</sup> Cough impairment is also considered critically  
122 important, as insufficient removal of airway secretions may result in the development of mucus  
123 plugging and complications such as atelectasis or pneumonia.<sup>15 16</sup> Effective coughing comprises an  
124 inspiration, compression and expulsion phase. Cough impairment following SCI may affect each  
125 phase due to the weakening of inspiratory and expiratory muscle function, which may decrease the  
126 maximum volume of expelled air by restricting both the maximum inspiratory volume prior to  
127 contraction as well as a reduction in the amount able to be expelled.<sup>15 17</sup> The limited evidence in SCI  
128 suggests that inspiratory (using maximal inspiratory muscle pressure;  $PI_{max}$ ) rather than expiratory



1  
2  
3 129 function (maximal expiratory muscle pressure;  $PE_{max}$ ) is the prime determinant of cough capacity  
4  
5 130 (peak flow), particularly in patients with a motor-complete cervical SCI.<sup>18</sup> Postma et al. found that  
6  
7 131 impaired pulmonary function may increase respiratory infections at one year after SCI, but their study  
8  
9 132 did incorporate respiratory muscle strengthening and respiratory complications were incompletely  
10  
11 133 assessed.<sup>7</sup>

12  
13 134  
14 135 To the best of our knowledge, there is currently no comprehensive database available for the further  
15  
16 136 development of generalizable prognostic models, nor to improve causal inference of pneumonia risk in  
17  
18 137 light of impairment in respiratory function. The multicenter and multinational cohort study RESCOM  
19  
20 138 aims to establish such an evidence base in SCI. We believe RESCOM will thereby improve clinical  
21  
22 139 practice through better targeting of interventions during the inpatient setting in high-income countries.  
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## 26 141 **METHODS AND ANALYSES**

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28 142

### 30 143 **Design and setting**

31  
32 144 RESCOM is a prospective international, multi-center cohort study in high income countries. Data  
33  
34 145 collection commenced in October 2016 across 10 specialized rehabilitation centers for SCI from  
35  
36 146 Austria (2 centers), Australia (1 center), Germany (1 center), The Netherlands (2 centers) and  
37  
38 147 Switzerland (4 centers) and is still ongoing.

39 148

### 41 149 **Study population**

42  
43 150 Newly injured persons who are aged 18 years or older, admitted for inpatient rehabilitation in the  
44  
45 151 participating centers, with complete or incomplete lesions (grades A-D on the American Spinal Injury  
46  
47 152 Association Impairment Scale (AIS)<sup>19</sup> and cervical or thoracic lesion levels (right and left motor level  
48  
49 153 between C1- T12). Persons with severe pre-existing scoliosis, progressive neurological diseases, 24h  
50  
51 154 mechanical ventilation dependency until more than 3 months post injury or severe mental disorders  
52  
53 155 are excluded.

54  
55 156

### 56 157 **Sample Size**

57  
58 158 For the analysis of pneumonia risk we estimated, over a conservative range of pneumonia event  
59  
60 159 probabilities from 0.1 to 0.2, the minimal sample size needed to detect a plausible hazard ratio (effect

1  
2  
3 160 size of interest) of 1.7 or more for inspiratory muscle strength (principal predictor variable).<sup>20</sup> Using a  
4  
5 161 conventional power of 0.8 and significance level of 0.05, this analysis indicated a sample size of 500  
6  
7 162 as adequate for the purpose of the present study.  
8  
9 163

10

### 11 164 **Procedures**

12 165 The measurement schedule of RESCOM includes up to four measurement time-points (T1-T4) during  
13  
14 166 the inpatient rehabilitation period (Figure 1). Following start of rehabilitation, newly injured patients are  
15  
16 167 contacted for recruitment at about 4 weeks (T1) or at 12 weeks (T2) if the first six or more weeks  
17  
18 168 following injury were spent on the ICU or in a general hospital for acute care. Subsequent  
19  
20 169 assessments are planned at 24 weeks (T3) and at discharge to the community (T4). The T4 timepoint  
21  
22 170 may precede and replace T2 and/or T3 in patients with a shorter length of inpatient rehabilitation stay.  
23  
24 171 Temporal start and length of inpatient stay for rehabilitation varies with injury severity, general health  
25  
26 172 status of patients and between countries and clinics. As such, between two and four measurement  
27  
28 173 time-points are anticipated across patients, with those with more severe lesions and the longest length  
29  
30 174 of stay providing more time points. In the four Swiss centers RESCOM is run as a “nested project” of  
31  
32 175 the Swiss Spinal Cord Injury (SwiSCI) cohort study ([www.swisci.ch](http://www.swisci.ch)).<sup>20</sup> The temporal schedule of data  
33  
34 176 collection of RESCOM is aligned to that of SwiSCI and the relevant data for RESCOM will be  
35  
36 177 extracted from the SwiSCI database additionally to RESCOM specific measurements and  
37  
38 178 questionnaires.  
39

40

### 41 179 42 43 180 **Quality control**

44  
45 181 Each of the participating centres has one or two responsible study nurses. Before the start of  
46  
47  
48 182 recruitment, a study nurse meeting in the Swiss Paraplegic Centre Nottwil was performed to train all  
49  
50 183 study nurses for the procedures and the assessments of the study. A study manual has been  
51  
52 184 established to give an overview of the procedures and all assessed variables. A frequently asked  
53  
54 185 question sheet is available in the study specific database (secuTrial®, iAS, Berlin, Germany) with all  
55  
56 186 relevant questions the study nurses asked during data collection. For quality control of data  
57  
58 187 assessment, regular central (database secuTrial®) and one local monitoring visit in each of the  
59  
60 188 participating centers are performed. The coordinating study center supports one central study

1  
2  
3 189 coordinator who is responsible for central and local monitoring as well as for support of the local study  
4  
5 190 nurses for questions concerning patient inclusion, data collection and entry into the database.

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8  
9 192 **Parameters assessed**

10  
11 193 *Primary outcome*

12 194 The occurrence of pneumonia is the primary outcome of RESCOM, observed continuously during the  
13  
14 195 whole risk period of interest from time of injury until the end of inpatient rehabilitation. Medical records  
15  
16 196 of inpatients are screened for diagnosis of pneumonia, including records from the acute care phase  
17  
18 197 before admission to the rehabilitation center. Pneumonia is classified by type and cause, and the date  
19  
20 198 of onset and duration of each event is recorded. Pneumonia is clinically diagnosed using the criteria  
21  
22 199 described in the pneumonia flow diagram as endorsed by the Center for Disease Control and  
23  
24 200 Prevention (CDC).<sup>21</sup> Mortality is defined as pneumonia-related, if pneumonia was clinically recorded as  
25  
26 201 the initiating cause of events leading to death. Other causes of death are similarly classified.

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29  
30 203 *Participant characteristics*

31 204 All participant characteristics are obtained from medical records. Basic characteristics that are  
32  
33 205 collected at T1 include gender, age, height, cause of SCI (traumatic or non-traumatic) and smoking  
34  
35 206 history. Parameters that may temporally vary, including body weight, motor lesion level and American  
36  
37 207 Spinal Injury Association Impairment Scale (AIS), medication, frequency of defecation as well as  
38  
39 208 medical complications are assessed on all available measurement time-points. At T4, the actual  
40  
41 209 smoking status and ICD-10 coded co-morbidities are recorded additionally.

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45 211 *Additional parameters*

46  
47 212 Additional parameters assessed at all measurement time-points, i.e. up to four times per participant  
48  
49 213 (further details on these measurements and questionnaires are given below):

- 50  
51 214 - Measurement of respiratory muscle strength and lung function  
52  
53 215 - ISCoS Pulmonary function data set<sup>22</sup>  
54  
55 216 - Quantitative questionnaire on physical exercise training  
56  
57 217 - Quantitative questionnaire on respiratory therapy and respiratory muscle training  
58  
59 218 - Bogenhausener Dysphagia score (BODS)  
60  
219 - ISCoS Quality of Life questionnaire <sup>23</sup>

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2  
3 220 - COVID-19 assessment form  
4

5 221

6  
7 222 *Measurement of respiratory function*

8  
9 223 Measurement of respiratory function consists of respiratory muscle strength (maximal inspiratory  
10  
11 224 pressure ( $PI_{max}$ ) and maximal expiratory pressure ( $PE_{max}$ ) and lung function with forced vital capacity  
12  
13 225 (FVC), forced expiratory volume in 1s ( $FEV_1$ ), peak expiratory flow (PEF) and peak cough flow (PCF).  
14  
15 226 All measurements are performed at the same day according to the ATS/ERS guidelines<sup>24</sup> in a sitting  
16  
17 227 position either in the participant's own wheelchair or on a chair in participants that are able to walk. To  
18  
19 228 derive a reliable estimate of the highest value for each parameter, each measurement is repeated until  
20  
21 229 the three highest values of a given parameter are within a 20% range. The highest value of each  
22  
23 230 parameter is retained for further analysis.<sup>25</sup>

24 231

25  
26 232 Measurement of respiratory muscle strength and lung function have been harmonized across the 10  
27  
28 233 centers using identical equipment.  $PI_{max}$  and  $PE_{max}$  are measured using a hand-held respiratory  
29  
30 234 pressure meter (Micro RPM, Micro Medical, Hoechberg, Germany). The  $PI_{max}$  measurement is derived  
31  
32 235 from residual volume and  $PE_{max}$  from total lung capacity, against the occluded one-way valve of the  
33  
34 236 respiratory pressure meter with the pressure maintained for at least one second. To derive the  
35  
36 237 maximum pressure over a one second period, the patient is instructed to maintain in- and expiratory  
37  
38 238 pressure for at least 1.5 seconds.<sup>26</sup> Abdominal binders are removed prior to any measurement of  
39  
40 239 respiratory function.<sup>27</sup>

41 240

42  
43 241 The FVC is the total volume of air the participant is able to exhale after a maximal inspiration. The  
44  
45 242  $FEV_1$  is the total volume of air that has been exhaled at the end of the first second of maximal forced  
46  
47 243 expiration. PEF is the maximum flow of air achieved during the maximum expiratory flow manoeuvre.  
48  
49 244 <sup>28</sup> During the PCF manoeuvre the maximum flow of air is measured by having the participant cough as  
50  
51 245 forcefully as possible through a peak flow meter. Participants breathe through a mouthpiece while  
52  
53 246 wearing a nose clip. Across study centers, lung function parameters are measured accordingly, but  
54  
55 247 using three different brands of portable spirometer, including Micro Loop® (Care Fusion, Basingstoke,  
56  
57 248 UK; all Swiss, Dutch and German centers), EasyOne Spirometer® (Niche Medical, Melbourne,  
58  
59 249 Australia; Australian center), Masterscreen PFT Pro® (Care Fusion, Hoechberg Germany; one  
60  
250 Austrian center) and Vitalograph® (Ennis, Ireland; one Austrian center).

251

*ISCoS Pulmonary function data set*

The ISCoS Pulmonary function data set<sup>22</sup> 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.

256

*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.

267

*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.

276

*ISCoS quality of life questionnaire*

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

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5 283 *COVID-19 assessment form*

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7 284 At the start of the COVID-19 pandemic (March 2020) we implemented an additional form into the study  
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9 285 database and instructed all study nurses of each participating center to additionally fill in this form for  
10  
11 286 the already included and future patients. Since COVID-19 infections are often leading to severe  
12  
13 287 pneumonia and probably also death, we identified this as a potential confounder of our study results  
14  
15 288 and therefore have to include this infection into our analysis. The COVID-19 form includes  
16  
17 289 information on diagnosis, date of diagnosis, symptoms and death due to COVID-19.

18 290

19  
20 291 **Database secuTrial®**

21  
22 292 To enable secure capture and management of RESCOM data, the professional and web-browser  
23  
24 293 based database system secuTrial® is used. SecuTrial® fulfills the minimal requirements for data  
25  
26 294 storage and management indicated in the ICG-GCP guidelines and also supports the central  
27  
28 295 monitoring of data collection across all participating centers. Database set-up, personal accounts with  
29  
30 296 pre-defined roles for all study collaborators as well as support, data export and archiving is provided  
31  
32 297 by a study-independent database manager from the study-center in Nottwil, Switzerland.

33 298

34  
35 299 **Methods of minimizing bias**

36  
37 300 Study participants receive an introduction for the study procedure by the local study nurse skilled in  
38  
39 301 the management of persons with SCI and trained for all study specific tasks. A standardized study  
40  
41 302 protocol was defined to minimize attrition bias.

42  
43 303 The coding of the participants is conducted by the study nurses of each site in order to keep the data  
44  
45 304 management and the biostatistician blinded (de-identified at source). The coding list remains with the  
46  
47 305 study nurses of each site for the whole duration of the study and archiving period. Thus, coding is  
48  
49 306 conducted without any influence of the principal investigator, the data manager or biostatistician. The  
50  
51 307 study investigators strive for complete separation of the persons involved in the steps of enrolment  
52  
53 308 and data collection from those involved in the data management and analysis.

54  
55 309 All assessments are conducted and entered into the study database by the trained study nurse(s) of  
56  
57 310 each participating center.

58 311

59  
60 312 **Patient and Public Involvement**

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2  
3 313 No patients or public have been directly involved in the planning or conduct of this study. Study results  
4  
5 314 will be disseminated to the scientific community through peer-reviewed journals and conference  
6  
7 315 presentations, to the SCI community, other stakeholders and via social media, newsletters and  
8  
9 316 engagement activities.

10  
11 317

## 12 318 **Statistics**

14 319 Statistical analysis will involve basic descriptive statistics and multivariable regression analyses that  
15  
16 320 take into account the longitudinal and multilevel structure of the data. A global overview of the  
17  
18 321 multivariable data analysis plan for investigating the association between respiratory function and  
19  
20 322 pneumonia is given in Figure 2. To evaluate variation in pneumonia risk, time-to-event analysis  
21  
22 323 techniques (e.g., flexible parametric survival modeling) will be employed, taking date of injury as the  
23  
24 324 starting point of the risk period. Regression models targeting causal inference will make use of time-  
25  
26 325 updated information for all variables in accordance with the repeated measurement schedule of  
27  
28 326 RESCOM, while controlling for between-person and between-center sources of variance using random  
29  
30 327 and fixed effects. The exposure 'respiratory function' will be operationalized using parameters of  
31  
32 328 respiratory muscle strength and parameters of lung function, as a latent construct within generalized  
33  
34 329 latent variable modeling or as individual parameters in selected analysis as required.<sup>29</sup> Critical  
35  
36 330 confounders that have been defined using evidence from the literature and expert opinion of RESCOM  
37  
38 331 collaborators include age, lesion severity, time since injury (structurally captured in time-to-event  
39  
40 332 modelling), artificial ventilation and medication. Models targeting prognosis of pneumonia during first  
41  
42 333 rehabilitation will only include parameters of respiratory function that have been collected at baseline.<sup>30</sup>

43 334 <sup>31</sup>

44  
45 335

## 47 336 **ETHICS AND DISSEMINATION**

48  
49 337 Full ethical approval for this project has been obtained by all local ethics committees of all participating  
50  
51 338 centers. We certify that all applicable institutional and governmental regulations concerning the ethical  
52  
53 339 use of data of human volunteers are followed during the course of this research.

54  
55 340 Potential protocol modifications and amendments will be submitted to the ethical committees for  
56  
57 341 approval. This project has been registered with ClinicalTrials.gov NCT02891096 and regular study  
58  
59 342 updates are presented on Research Gate ([https://www.researchgate.net/project/RESCOM-  
60 343 RESpiratory-COMplications-after-Spinal-Cord-Injury](https://www.researchgate.net/project/RESCOM-RESpiratory-COMplications-after-Spinal-Cord-Injury)).

1  
2  
3 344 All participants give written or witnessed verbal consent if upper limb function is too impaired for a  
4  
5 345 participant to sign, prior to entering the study.

6  
7 346 The study results will be disseminated through publication in scientific journals, presentation at  
8  
9 347 relevant conferences, directly to the participants and clinicians as well as on social media and in  
10  
11 348 newsletters. The dissemination aims to provide clinicians with reliable prognostic factors to identify  
12  
13 349 persons who are at heightened risk of pneumonia and thus, to effectively reduce pneumonia risk and  
14  
15 350 pneumonia-related hospitalizations.

16 351

## 17 352 **STRENGTH AND LIMITATIONS**

18  
19  
20 353 RESCOM is the first prospective, international study that reports modifiable predictors of pneumonia  
21  
22 354 from a representative sample of persons with SCI during inpatient rehabilitation. Its comprehensive  
23  
24 355 evidence base facilitates the systematic evaluation of the discriminatory power of respiratory function  
25  
26 356 parameters for pneumonia risk in high income countries.

27  
28 357 The RESCOM study is effective in recruiting a representative sample of inpatients with a motor  
29  
30 358 complete or incomplete SCI in Austria, Australia, Germany, The Netherlands and Switzerland. The  
31  
32 359 anticipated minimal sample size of 500 should provide project sufficient statistical power to answer the  
33  
34 360 key hypothesis that respiratory function, and  $PI_{max}$  in particular, is a strong prognostic parameter that  
35  
36 361 quantifies clinical pneumonia risk in SCI. The longitudinal, international design of this project is  
37  
38 362 considered a further strength; participants can be observed during the whole period of inpatient  
39  
40 363 rehabilitation in different countries. Various factors like a central web-based database, a study nurse  
41  
42 364 meeting, a comprehensive study manual and regular monitoring were implemented to ensure the  
43  
44 365 standardization of the measurements and data and thus to keep quality of the project in the 10 centers  
45  
46 366 as high as possible.

47 367

48  
49 368 For data collection we used the International SCI Core Data Set,<sup>32 33</sup> the International SCI QoL Basic  
50  
51 369 Data Set<sup>23</sup> and the International SCI Pulmonary Function Data Set<sup>22</sup> which are developed to provide  
52  
53 370 global data standards for SCI clinical research. The advantage of using these standardized data sets  
54  
55 371 is to increase the data quality and to facilitate data sharing.

56  
57 372 Potential limitations include the observational nature of the project which limits causal inference even  
58  
59 373 within a prospective study design. Although the RESCOM sample reflects the composition of the  
60  
374 source population quite well, we cannot exclude potential selection bias and therefore, the results of



1  
2  
3 375 the RESCOM project may not be transferable to all persons with SCI. There is a risk that the study  
4  
5 376 inclusion and exclusion criteria may miss those patients with a potential high risk of pneumonia  
6  
7 377 because those with more severe lesions or more complications may not consent to participate in an  
8  
9 378 observational study that may not directly increase their outcome. Similarly, patients with a very long  
10  
11 379 stay in the intensive care unit (e.g. due to polytrauma) or a very late admission to the rehabilitation  
12  
13 380 unit, may miss T2 and therefore no more qualify for study participation. Those patients with 24h of  
14  
15 381 mechanical ventilation are excluded since respiratory function cannot be measured and also those  
16  
17 382 with other languages than used in our study centers are excluded. Another limitation of this project is  
18  
19 383 that we do not have a follow-up period after the participants complete inpatient rehabilitation.

20 384  
21  
22 385 In summary, using discriminatory parameters of respiratory function, clinicians may identify persons  
23  
24 386 with SCI who are at heightened risk of developing pneumonia during inpatient rehabilitation. Thus,  
25  
26 387 interventions can be targeted at these persons to reduce pneumonia risk. The RESCOM study is well-  
27  
28 388 positioned to determine prognostic parameters of respiratory function for pneumonia risk in SCI.

1  
2  
3 389 **Acknowledgements**

4  
5 390 The authors are grateful to all the participants of the RESCOM study and all the study nurses for their  
6  
7 391 great work in recruitment and data collection. The authors also acknowledge the financial support from  
8  
9 392 Wings for Life (WFL-CH-014/16) and the Swiss Paraplegic Foundation for the SwiSCI nested project  
10  
11 393 start-up grant.

12 394  
13  
14 395 **Collaborators**

15  
16 396 This study offers options of scientific collaborations.  
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18 397

19  
20 398 **Author Contributions**

21  
22 399 GM is the principal investigator of the RESCOM project. AMR and GM designed the study. MWGB  
23  
24 400 provided statistical and methodological support. DJB, KP, DG, SH, MTEH, BH, MHG, XJ, MS and RW  
25  
26 401 provided clinical support and/or are responsible for data collection in their respective clinics. AMR,  
27  
28 402 MWGB and GM drafted the work and DJB, KP, DG, SH, MTEH, BH, MHG, XJ, MS and RW revised it  
29  
30 403 critically for important intellectual content. AMR was responsible for the monitoring-visits. All authors  
31  
32 404 approved the final version of the manuscript and agreed to be accountable for all aspects of the work.  
33  
34 405

35 406 **Data Availability Statement**

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37 407 After completion of data collection and analysis, all relevant data and estimates of this study will be  
38  
39 408 deposited on Dryad.  
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41 409

42  
43 410 **Funding**

44  
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48  
49 413 SwiSCI nested project start-up grant of the Swiss Paraplegic Foundation.  
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51 414

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53 415 **Competing Interests**

54  
55 416 The authors declare no conflict of interest.  
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57 417

58 418 **Patient consent**

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60 419 Obtained.

420

421 **Registration**

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

425

426 Ethics approval: Approved by all local ethics committees of all participating centers, namely: for  
427 Switzerland: ethics committee north-west and central Switzerland (EKNZ) for the two Swiss Centres  
428 SPZ Nottwil and REHAB Basel, ethics committee Zurich, Switzerland for the Balgrist, Zurich and  
429 Ethics Committee Vaud, Switzerland for the CRR Sion (Nr. 2016-01065 – one multi-centric application  
430 for all Swiss centres). In Germany from the 'Ethikkommission der Ärztekammer Hamburg' (Nr. PV  
431 5502); for Austria from the 'Ethikkommission der Medizinischen Universität Innsbruck' (Nr. AN-2016-  
432 0176) and the 'Ethikkommission für die Krankenanstalten der AUVA' (Nr. 6/2016). In the Netherlands  
433 from the medical ethics committee of the Erasmus Medical Centre Rotterdam (Nr. MEC-2016-594)  
434 and for Australia from the Austin Health Human Research Ethics Committee (Nr. LNR/16/Austin/422).

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3 536 **FIGURE LEGENDS**  
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7 538 **Figure 1**

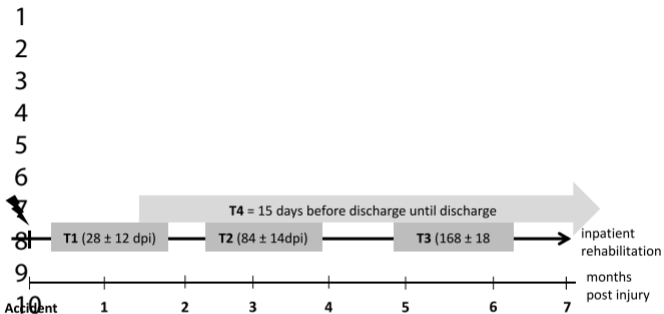
8  
9 539 Time frames for measurements (T1 to T4) during inpatient rehabilitation. T1-T3 time-windows with days  
10 540 post injury (dpi) are shown by blue bars and T4 by the green bar above.  
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15 543 **Figure 2**

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17 544 Global scheme of the planned data analysis investigating the dynamic association between respiratory  
18 545 function and pneumonia. In regression modelling all variables will be time-updated in accordance with  
19 546 the repeated measurement schedule of RESCOM and controlling for between-person and between-  
20 547 center sources of variance. Respiratory function is operationalized using parameters of respiratory  
21 548 muscle strength and parameters of lung function.  
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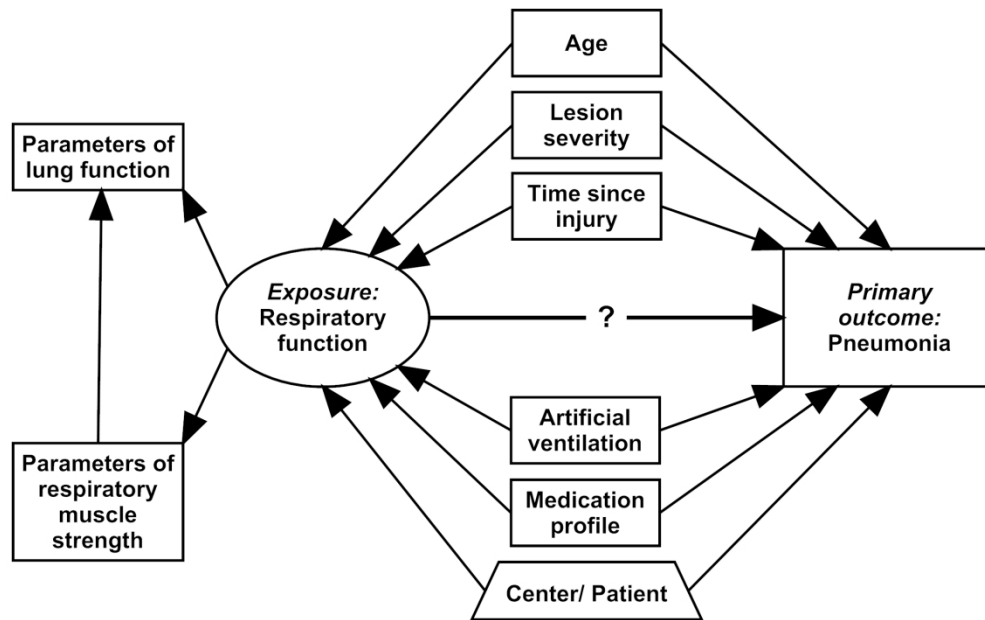


Figure 2

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.



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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract  (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1  3
<b>Introduction</b>			
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
<b>Methods</b>			
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  (b) For matched studies, give matching criteria and number of exposed and unexposed	6/7  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  (b) Describe any methods used to examine subgroups and interactions  (c) Explain how missing data were addressed  (d) If applicable, explain how loss to follow-up was addressed  (e) Describe any sensitivity analyses	11  11/Fig.2 n.a. n.a. n.a.
<b>Results</b>			
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  (b) Give reasons for non-participation at each stage  (c) Consider use of a flow diagram	n.a. since this is a protocol paper
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  (b) Indicate number of participants with missing data for each variable of interest	n.a. since this is a protocol paper

		(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
<b>Discussion</b>			
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
<b>Other information</b>			
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>.