The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function

Jan Mehrholz, 1, 2 Simone Mückel, 1 Frank Oehmichen, 3 Marcus Pohl 3

ABSTRACT

Introduction: Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive care unit (ICU)-acquired muscle weakness. This weakness of limb muscles increases morbidity and delay rehabilitation and recovery of walking ability. Although full recovery has been reported people with severe weakness may take months to improve walking. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood. Therefore, the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe the time course of recovery of walking function and other activities of daily living in these patients.

Methods and analysis: We conduct a prospective cohort study of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP. Based on our sample size calculation, approximately 150 patients will be recruited from the ICU of our hospital in Germany. Amount and content of physical rehabilitation, clinical tests for example, muscle strength and motor function and neuropsychological assessments will be used as independent variables. The primary outcomes will include recovery of walking function and mobility. Secondary outcomes will include global motor function, activities in daily life and participation.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and conducted with the approval of the local medical Ethics Committee (Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1) and with the understanding and written consent of each patient’s guardian. The results of this study will be published in peer-reviewed journals and disseminated to the medical society and general public.

INTRODUCTION

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive care unit acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterised by a profound weakness that is greater than might be expected to result from prolonged bed rest. 1 The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit to stand or sitting and standing is oftentimes required. 2–4 This increases morbidity and delays rehabilitation and recovery of walking. 5,6 Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition for example, people with severe weakness may take months to improve, or even remain severely affected. 7,8 Focused physical rehabilitation of people with
ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature. However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of daily life. Furthermore a multivariate model for recovery of walking ability will be developed.

METHODS AND ANALYSIS

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily life.

Secondary objectives are to:

- Describe the concomitant physical rehabilitation therapies;
- Describe the clinical course of recovery using standardised outcome measures and their results;
- Identify a prognostic model for regain walking and sit to stand abilities.

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow-up will be made in 2015.

Based on our sample size calculation, approximately 150 patients will be recruited from a ICU of our hospital in Germany. over the course of 3 years. In a first cross-sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within 3 years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the ICUs of our acute care, weaning and early rehabilitation centres of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- Patient is chronic critical ill or has a contemporary history of chronic critical ill-defined as more than 21 days ICU-treatment including mechanical ventilation and at least 14 days further existing critical situation with the need for ICU-treatment;
- Defined diagnosis of CIM and CIP. The diagnosis of CIM/CIP will be confirmed by a neurologist. Therefore, clinical and neurophysiological data will be revealed. The procedure of diagnosis of CIP and CIM is described in detail elsewhere;
- Muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points;
- More than 18 years old;
- Richmond Agitation Sedation Scale (RASS) score from −1 to 2;
- Written informed consent of the patient or his legal guardian.

Exclusion criteria

- Patients receiving palliative care;
- Comorbidities of the trunk or the lower limbs interfering with upright posture and walking function (eg, amputation or fracture of lower limb);
- Other neuromuscular or neurological disease and/or syndromes causing weakness in patients in the ICU (we will exclude patients with diseases and syndromes causing weakness in patients in the ICU due to Guillain-Barré syndrome, myasthenia gravis, porphyria, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, vasculitic neuropathy, cervical myelopathy and botulism);
- Severe physical comorbidity before becoming critical ill (eg, frailty due to neurological conditions).

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the demographic and clinical characteristics will be measured (baseline assessment T0). Patients will then be measured every 2 weeks after baseline up to 20 weeks (week 2 (T1), week 4 (T2), week 6 (T3), week 8 (T4) week 10 (T5) and so on until week 20 (T10)). Two follow-ups are planned: FU1 after 6-month and FU2 after 1 year after study entry. For follow-up assessments
(FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate. The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets. All assessments and standardised measures will be administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility. Additionally, we will try to get all information about the content and duration of physiotherapy and or physical rehabilitation applied at all stages of illness.

Measures and outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the functional ambulation categories (FAC) is used. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height). Secondary outcomes includes:

▸ Richmond Agitation-Sedation Scale (RASS)
▸ Activities measured with the Barthel Index (BI; 10 items)
▸ Muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC)
▸ Grip strength (measured bilaterally using a dynamometer)
▸ Functional Status Score for the Intensive Care Unit Scored (FSS-ICU)
▸ Physical Function–ICU Test (PFIT) and Physical Function–ICU Test-Scored (PFIT-S)
▸ Pain using a visual analogue scale
▸ Lateral and frontal sit and stance balance (functional reach)
▸ Cognitive measures (Montreal Cognitive Assessment (MoCA) and clock drawing test (CDT))
▸ Walking ability (0–5; FAC), walking speed (we will use a 10 m walking test, adopting a 14 m course and will measure the walking speed over the central 10 m) and walking endurance (we will use a 6 min walking test, using 40 m course and will measure the distance walked in 6 min; if patients cannot walk the whole 6 min we will measure the maximum walking distance here)
▸ Quality of life (EQ-5D)
▸ Participation (Reintegration to Normal Living, RNL-Index)
▸ Fitness and mobility (PASIPD)

All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardised sheets for this purpose.

At baseline assessment (T0) and then every 2 weeks until 20 weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow-ups FU1 after 6-month and FU2 after 1 year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Table 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics (such as diagnoses, reason for ICU-treatment, duration of mechanical ventilation, duration of illness) and anthropometric measures, such as body weight and body mass index (but not limb circumference).

Planned statistical analyses

We will use descriptive analyses, for example, means and SDs of the continuous variables and frequencies and proportions of categorical variables as appropriate. We will explain differences across the time points (T1–T10 and FU1–FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate for example, repeated measures analysis of variance. The global α level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analysed for their association with these end points:

▸ demographic variables (such as age and sex);
▸ clinical variables (such as muscle strength, FSS-ICU, PFIT-S);
▸ medical characteristics (such as diagnosis and duration of illness).

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor. A stepwise multivariable Cox regression analysis will be applied with a variable selection.

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance. The final model selection will be performed based on clinical decision, together with Akaike’s information criterion (AIC) and
Aim of our analysis is to explain the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables. To prevent overfitting, only variables with clinically important and statistically significant bivariate association with our end point will be included in the final model.

The effects of prognostic factors in the final model will be expressed as HRs with 95% CIs after a graphical assessment of proportionality of hazards. We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc, Cary, North Carolina, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

**Results**

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1–FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

**Sample size and power calculation**

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the ‘rule of ten events per variable (EPV)’. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the ICU of our long-term intensive care hospital in Germany. We anticipate reaching this study size over the time course of 3 years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our ICUs. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within 3 years of recruitment.

**ETHICS AND DISSEMINATION**

**Ethical considerations**

The GymNAST study will be conducted in accordance with the ‘Helsinki Declaration’. The study is non-invasive, imposes no risk on patients, seems to have the Bayesian information criterion (BIC). Aim of our analysis is to explain the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

| Table 1  | Summary of outcome measures and time points of assessment in GymNAST |
|---------|---------------------------------------------------------------|
|         | Baseline | Daily | Biweekly (T1 to T10) | Follow-up (FU 1 and 2) |
| Amount and content of physical rehabilitation |          |       |                   |                      |
| Physiotherapy | x        | x     |                   |                      |
| Occupational therapy | x        |       |                   |                      |
| Other therapies (eg, groups) | x        |       |                   |                      |
| Primary outcome |          |       |                   |                      |
| FAC and STS | x        | x     |                   |                      |
| Delir measures |          |       |                   |                      |
| RASS | x        |       |                   |                      |
| Strength measures |          |       |                   |                      |
| MRC score | x        | x     |                   |                      |
| Grip strength | x        |       |                   |                      |
| Physical function measures |          |       |                   |                      |
| PFIT and PFIT-S | x        | x     |                   |                      |
| FSS-ICU score | x        |       |                   |                      |
| 10 m walking time | x        | x     |                   |                      |
| 6-MWT | x        |       |                   |                      |
| Pain (VAS) | x        |       |                   |                      |
| Functional reach | x        |       |                   |                      |
| Cognition measures |          |       |                   |                      |
| MOCA | x        | x     |                   |                      |
| CDT | x        |       |                   |                      |
| Activities and Mobility |          |       |                   |                      |
| BI | x        | x     |                   |                      |
| PASIPD | x        |       |                   |                      |
| Participation and quality of life |          |       |                   |                      |
| EQ-5D |         |       |                   |                      |
| RNL-Index | x        |       |                   |                      |

6-MWT, 6 min walking test; BI, Barthel Index; CDT, clock drawing test; EQ-5D, EuroQol (5 dimensions); FAC, functional ambulation; FSS-ICU, Functional Status Score for the Intensive Care Unit Scored; FU, follow-up; GymNAST, General Weakness Syndrome Therapy study; MOCA, Montreal Cognitive Assessment; MRC, Medical Research Council (muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle)); PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; PFIT, Physical Function—Intensive Care Unit-Test; PFIT-S, Physical Function—Intensive Care Unit Test-Scored; RASS, Richmond Agitation-Sedation Scale; RNL-Index, Reintegration to Normal Living Index; STS, ability to stand up from a chair independently; T, time point; VAS, visual analogue scale.

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the ‘rule of ten events per variable (EPV)’. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the ICU of our long-term intensive care hospital in Germany. We anticipate reaching this study size over the time course of 3 years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our ICUs. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within 3 years of recruitment.

**Sample size and power calculation**

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the ‘rule of ten events per variable (EPV)’. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the ICU of our long-term intensive care hospital in Germany. We anticipate reaching this study size over the time course of 3 years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our ICUs. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within 3 years of recruitment.
enough power to detect meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

**Dissemination**
The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

**DISCUSSION**
The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of 1 year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups and only some studies measures continuously over time. However, instead of comparing two or more measurements of the patient’s performance it seems to be more informative to analyse the dynamic recovery systematically using equal time intervals over an appropriate time period for example, with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (eg, clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every 2 weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalise the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or MR tomography will be used.

**Contributors** JM, SM, FO and MP planned the study. FO and MP contributed to the procurement of funding. JM, SM and MP developed the protocol. All authors contributed to and checked the final draft of the manuscript.

**Funding** This study is financially supported by the Centre of Research from Klinik Bavaria, Kreischa, Germany and by the Department of Public Health, Medizinische Fakultät, Carl Gustav Carus’, Technische Universität Dresden, Germany.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**REFERENCES**

1. Nordon-Craft A, Moss M, Quan D, et al. Intensive care unit-acquired weakness. Phys Ther 2012;92:1494–506.
2. Fan E. Critical illness neuromyopathy and the role of physical therapy and rehabilitation in critically ill patients. Respir Care 2012;57:933–44; discussion 944-6.
3. Herridge MS. The challenge of designing a post-critical illness rehabilitation intervention. Crit Care 2011;15:1002.
4. Ohtake PJ, Stracher DC, Needham DM. Rehabilitation for people with critical illness: taking the next steps. Phys Ther 2012;92:1484–8.
5. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:883–93.
6. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293–304.
7. Hermans G, De Jonghe B, Bruyninckx F, et al. Clinical review: critical illness polyneuropathy and myopathy. Crit Care 2008;12:238.
8. Kress J, Hall J. ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014;370:1626–35.
9. Denehy L, Berney S, Skinner E, et al. Evaluation of exercise rehabilitation for survivors of intensive care: protocol for single blind randomised controlled trial. Open Crit Care Med J 2009;1:39–47.
10. Denehy L, Berney S, Skinner E, et al. Evaluation of exercise rehabilitation for survivors of intensive care: protocol for single blind randomised controlled trial. Open Crit Care Med J 2009;1:39–47.
11. Denehy L, Skinner E, Holder D, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months follow up. Crit Care 2013;17:R156.
12. Nordon-Craft A, Schenkenman M, Ridgeway K, et al. Physical therapy management and patient outcomes following ICU-acquired weakness: a case series. J Neurol Phys Ther 2011;35:133–40.
13. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–10.
14. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per independent variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–18.
15. Mallett S, Royston P, Dutton S, et al. Reporting methods in studies developing prognostic models in cancer: a review. BMC Med 2010;8:20.
16. Möckel S, Mehrholz K, Mehrholz J, et al. Treatment approaches of patients with ICU acquired weakness [Behandlungsansätze bei Patienten mit auf der Intensivstation erworbenen Schwächesyndrom]. Neuroreha 2013:5:40–3.
17. Oehmichen F, Ragaller M. Beamtungsentwöhnung bei Chronisch-Kritis-Kranken. Intensiv- und Notfallbehandlung 2012;37:118–26.
18. Oehmichen F, Pohl M, Schlosser R, et al. Critical-illness Polyneuropathie und -Polymyopathie: Wie sicher ist die klinische Diagnose bei Patienten mit Weaning-Failure? [Critical illness polyneuropathy and polymyopathy: how certain is the clinical diagnosis in patients with weaning failure?]. Nervenarzt 2012;83:220–5.

19. Latronico N, Rasulo FA. Presentation and management of ICU myopathy and neuropathy. *Curr Opin Crit Care* 2010;16:123–7.

20. Latronico N, Bolton C. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol* 2011;10:931–41.

21. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–44.

22. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Phys Ther* 1986;66:1530–9.

23. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *MD State Med J* 1965;14:61–5.

24. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain–Barre syndrome. *Muscle Nerve* 1991;14:1103–9.

25. Mathiowetz V, Weber K, Volland G, et al. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am* 1984;9:222–6.

26. Mathiowetz V, Kashman N, Volland G, et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985;66:69–74.

27. Zanni JM, Korupolu R, Fan E, et al. Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project. *J Crit Care* 2010;25:254–62.

28. Nordon-Craft A, Schenkman M, Edbrooke L, et al. The physical function intensive care test: implementation in survivors of critical illness. *Phys Ther* 2014;94:1499–507.

29. Denehy L, de Morton N, Skinner E, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function test in intensive care test (scored). *Phys Ther* 2013;93:1636–45.

30. Weiner DK, Duncan PW, Chandler J, et al. Functional reach: a marker of physical frailty. *J Am Geriatr Soc* 1992;40:205–7.

31. Newton RA. Validity of the multi-directional reach test: a practical measure for limits of stability in older adults. *J Gerontol A Biol Sci Med Sci* 2001;56:M248–52.

32. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.

33. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. *Int J Geriatr Psychiatry* 2010;25:111–20.

34. Holden MK, Gill KM, Magliozzi MR, et al. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Phys Ther* 1984;64:35–40.

35. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.

36. Wood-Dauphinee SL, O'Poomer MA, Williams JL, et al. Assessment of global function: the Reintegration to Normal Living Index. *Arch Phys Med Rehabil* 1998;69:583–90.

37. Wood-Dauphinee S, Williams JL. Reintegration to normal living as a proxy to quality of life. *J Chronic Dis* 1987;40:491–502.

38. Salisbury LG, Merriweather JL, Walsh TS. Rehabilitation after critical illness: could a ward-based generic rehabilitation assistant promote recovery? *Nurs Crit Care* 2010;15:57–65.

39. van den Berg-Emons RJ, L'Ortey AA, Buffart LM, et al. Validation of the Physical Activity Scale for individuals with physical disabilities. *Arch Phys Med Rehabil* 2011;92:923–8.

40. Armitage P, Colton T. *Encyclopedia of biostatistics*. Chichester: Wiley, 1998.

41. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.

42. Kleinbaum D, Klein M. *Survival analysis*. 3rd edn. New York: Springer, 2012.

43. Hosmer D, Lemeshow S, May S. *Applied survival analysis: regression modelling of time to event data*. 2nd edn. New York: John Wiley & Sons, Inc., 2008.

44. Spiegelhalter DJ. Probabilistic prediction in patient management and clinical trials. *Stat Med* 1986;5:421–33.

45. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med* 2000;19:1059–79.

46. Hosmer DW, Lemeshow S. *Applied logistic regression*. 2nd edn. New York: John Wiley & Sons, Inc., 2000.

47. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874–82.