CRITICAL CARE AND RESUSCITATION

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Presneill JJ, Bellomo R, Brickell K, et al; TEAM Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Protocol and statistical analysis plan for the phase III randomised controlled TEAM trial: Treatment of invasively ventilated adults with Early Activity and Mobilisation *Crit Care Resusc* 2021; 23: 262-72. https://doi.org/10.51893/2021.3.OA3

Appendix 1. Abbreviations

ADL: Barthel Activities of Daily Living
AE: Adverse Events
ANZIC RC: Australian and New Zealand Intensive Care Research Centre
CAM-ICU: Confusion Assessment Method-ICU
CIs: Confidence Intervals
CONSORT: Consolidated Standards of Reporting Trials
DAOH: Days alive and out of hospital
DSMC: Data and Safety Monitoring Committee
EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level
ESM: Electronic Supplementary Material
EU: European Union
HADS: Hospital Anxiety and Depression Scale
HRQOL: Health Related Quality of Life
IADL: The Lawton Instrumental Activities of Daily Living Scale
ICCTN: Irish Critical Care Clinical Trials Network
ICNARC: Intensive Care National Audit & Research Centre
ICU: Intensive Care Unit
IES-R: Impact of Event Scale – Revised
IMS: ICU Mobility Scale
IMV: Invasive Mechanical Ventilation
ITT: Intention to treat
MRINZ: Medical Research Institute of New Zealand
MOCA-Blind: Montreal Cognitive Assessment
OECD: Organisation for Economic Cooperation and Development
QALYs: Quality Adjusted Life Years
RASS: Richmond Agitation-Sedation Scale
WHODAS: World Health Organisation's Disability Assessment Schedule

Appendix 2 Calculation of Primary outcome

Outline of specification within the R (24) package quantreg (25) of wild gradient bootstrap estimates for cluster-robust inference (26) in linear quantile regression models

```
#-------------------------------------------------------------------------------------
> library(quantreg)
> data(team3_rct)
> primaryoutcome <- rq(daoh180 ~ treatment_indicator, tau = 0.5, subset = NULL, weights = NULL, na.action = na.omit, model = TRUE, method = "br")
## or … treatment_indicator + unbalanced_baseline_variable1 + unbalanced_baseline_variable2 ….
> summary(primaryoutcome, se = "boot", cluster = team3_rct$site_id, R = 10000)
#-------------------------------------------------------------------------------------
```

Appendix 3 Relative power of alternative methods for analysis of the primary outcome

Power Calculations for Different Statistical Tests with Days Alive and Out of Hospital at Day 180 as the Outcome (Difference of 10 days)

Effect	$DAOH_{180}$[a]	Fine-Gray Model	Wilcoxon Rank-Sum Test[b]	Median Regression[c]			Cumulative Logistic Model
				Asymmetric Laplace	Simplex	Interior Point	
Driven by hospital length of stay in survivors							
Treatment	148.0 ± 47.9	95%	99%	98%	99%	99%	99%
Control	137.6 ± 40.1						
Driven by mortality							
Treatment	145.8 ± 33.0	80%	71%	63%	49%	49%	71%
Control	137.6 ± 40.1						
Driven by mortality and length of stay in survivors							
Treatment	148.9 ± 38.1	97%	99%	96%	96%	95%	99%
Control	137.6 ± 40.1						

The test with the highest power in each scenario is highlighted in bold.

All simulations based on the data from the pilot study (7), described below. The proposed scenarios were calculated varying mortality and/or length of stay (from the pilot study) to achieve a difference in $DAOH_{180}$ of around 10 days (close to the original sample size calculations, which were based on the pilot study (7) and a systematic review (16)).

- Intervention: mortality of 6.9% and hospital length of stay in survivors of 31.6 ± 26.8 days
- Control: mortality of 4.8% and hospital length of stay in survivors of 35.4 ± 26.2 days

All results based in 3,000 simulated trials with 375 subjects in each of two treatment groups, a two-sided alternative hypothesis, and a type I error rate of $\alpha = 0.05$.

[a] Mortality simulated according to a Bernoulli distribution and hospital length of stay in survivors according to a normal distribution.

[b] Normal approximation with continuity correction was used for the Wilcoxon rank-sum test.

[c] All p values extracted via bootstrap with 1000 samples.

Appendix 3 Continued Relative power of alternative methods for analysis of the primary outcome

Power Calculations for Different Statistical Tests with Days Alive and Out of Hospital at Day 180 as the Outcome (Difference of 5 days)

Effect	$DAOH_{180}$[a]	Fine-Gray Model	Wilcoxon Rank-Sum Test[b]	Median Regression[c]			Cumulative Logistic Model
				Asymmetric Laplace	Simplex	Interior Point	
Driven by hospital length of stay in survivors							
Treatment	143.3 ± 46.8	55%	95%	55%	93%	93%	95%
Control	137.6 ± 40.1						
Driven by mortality							
Treatment	143.2 ± 37.9	46%	53%	38%	37%	38%	53%
Control	137.6 ± 40.1						
Driven by mortality and length of stay in survivors							
Treatment	143.5 ± 40.1	51%	73%	37%	56%	58%	73%
Control	137.6 ± 40.1						

The test with the highest power in each scenario is highlighted in bold.

All simulations based on the data from the pilot study (7), described below. The proposed scenarios were calculated varying mortality and/or length of stay (from the pilot study) to achieve a difference in $DAOH_{180}$ of around 5 days (half the original sample size calculations, which were based on the pilot study (7) and a systematic review (16)).

- Intervention: mortality of 6.9% and hospital length of stay in survivors of 31.6 ± 26.8 days
- Control: mortality of 4.8% and hospital length of stay in survivors of 35.4 ± 26.2 days

All results based in 3,000 simulated trials with 375 subjects in each of two treatment groups, a two-sided alternative hypothesis, and a type I error rate of $\alpha = 0.05$.

[a] Mortality simulated according to a Bernoulli distribution and hospital length of stay in survivors according to a normal distribution.

[b] Normal approximation with continuity correction was used for the Wilcoxon rank-sum test.

[c] All p values extracted via bootstrap with 1000 samples.

Title: Treatment of invasively ventilated adults with Early Activity and Mobilisation (TEAM): a protocol for a phase III randomised control trial – Online Supplement

Authors:

The TEAM Study Investigators on behalf of the Australian and New Zealand Intensive Care Society Clinical Trial Group

Table of Contents

Appendix A. TEAM Study Management Committee:

The TEAM Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trial Group

Writing Committee: Jeffrey J Presneill[1,2] , , Rinaldo Bellomo[1,3] Kathy Brickell[4], Heidi Buhr[5], Belinda J Gabbe[6], Doug W Gould[7], Meg Harrold[8], Alisa M Higgins[1], Sally Hurford[9], Theodore Iwashyna[10], Ary Serpa Neto[1,11], Alistair Nichol[1,4], Stefan J Schaller[12], Janani Sivasuthan[1], Claire Tipping[13], Steven Webb[1,14], Paul Young[10,15,] Carol L Hodgson[1,13](Chair)

1. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.
2. Department of Critical Care, University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia.
3. Critical Care Department, Austin Hospital, Melbourne, VIC, Australia.
4. University College Dublin-Clinical Research Centre, St Vincent's Hospital, Dublin, Ireland.
5. The Royal Prince Alfred Hospital, Sydney, NSW, Australia.
6. School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.
7. Intensive Care National Audit and Research Centre, 14207, London, United Kingdom of Great Britain and Northern Ireland.
8. Curtin University, Perth, WA, Australia; Royal Perth Hospital, Perth, WA, Australia.
9. Medical Research Institute of New Zealand, Wellington, New Zealand
10. Department of Medicine, Division of Pulmonary & Critical Care, University of Michigan, Ann Arbor; Centre for Clinical Management Research, VA Ann Arbor Healthcare System, Michigan.
11. Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.
12. Charité - Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany.
13. Department of Physiotherapy, Alfred Health, Melbourne, Australia.
14. St. John of God Hospital, Subiaco, Western Australia, Australia; School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia.
15. Intensive Care Unit, Wellington Hospital, Wellington, New Zealand.

Appendix B. The TEAM Trial Investigators

Australia

Austin Hospital, VIC, Australia: Sue Berney, Ally Macdonell.

Barwon Health Geelong, VIC, Australia: Nima Kakho, Joseph McCaffrey, Tania Salerno, Matthew Thackeray, Tom Crawford, Allison Bone, Tania Elderkin, Jemma Trickey, Michelle Horton.

Cabrini Hospital, VIC, Australia: Deirdre Murphy, Shannon Simpson, Alyssa Waanders, Natasha Lade, David Brewster, Vineet Sarode, Steve Philpot, Annie Mirabile.

Caboolture Hospital, QLD, Australia: Mahesh Ramanan, Louisa Lightfoot, Roland Bartholdy, Jean Nel, Hannelie de Beer, Jacinta Weber.

Casey Hospital, VIC, Australia: Joanna Caruana

Dandenong Hospital, VIC, Australia: Michelle Paton, Maria Shenouda.

Epworth Hospital, VIC, Australia: Jonathan Barrett, Gabrielle Hanlon, Rachel Fielding.

John Hunter Hospital, NSW, Australia: Lauren Thomas, Sally Rose, Gabrielle van Balen, Amber-Louise Poulter.

Launceston General Hospital, TAS, Australia: Ianthe Boden, Lucy Dennis, Jane Lockstone, Sarah Mineall.

Mater Health, QLD, Australia: I. Anne Leditschke, Mackenzie Finnis, Katherine Jongebloed, Jennifer Murphy, Felicity Prebble.

Mater Private Hospital, QLD, Australia: I. Anne Leditschke, Mackenzie Finnis, Katherine Jongebloed Lauren Griffin, Donna Deans.

Monash Medical Centre, VIC, Australia: Shihoko Pearson

Princess Alexandra Hospital, QLD, Australia: Alicia Bowen, Marc Nickels, Danielle Ferguson, Robin Dyball, Melissa McKinnon.

Redcliffe Hospital, QLD, Australia: Morag Shealy, Sharne Neill, Louise Hodges, Mahesh Ramanan, Maree Duroux, Megan Ratcliffe.

Rockhampton Hospital, QLD, Australia: Helen Miles, Kirsty Watson, David Hamilton, Josephine Reoch, Travis Auty.

Royal Adelaide Hospital, SA, Australia: Benjamin Reddi, Stephanie O'Connor, Simone Dafoe, Kathleen Glasby, Justine Rivett, Nerissa Brown, Rocky Callisto, Anna Threadgold.

Royal North Shore Hospital, NSW, Australia: Celia Bradford, Raymond Raper, Naomi Diel, Simon Finfer, Roger Harris, Naomi Hammond, Frances Bass, Elizabeth Yarad, Leisl Davis, Amanda Sukkar, Angela Ashelford, Miyuki Tokumitsu, Anne O'Connor, Julia Pilowsky.

Royal Perth Hospital, WA, Australia: Julian Sunario, Emily Bilish, Sharon Waterson, Brittany Fergusson.

Royal Prince Alfred Hospital, NSW, Australia: Nazmeen Reddy, David Gattas, Heidi Buhr, Jennifer Coles.

St George Hospital, NSW, Australia: Wendy Chaseling, Jennene Miller, Deborah Inskip, Eva Zveglic, Manoj Saxena.

St Vincent's Hospital, VIC, Australia: Laura Sparkes, John Santamaria, Gemma Pound, Anna Shukla, Sophie Heywood.

Sunshine Coast University Hospital, QLD, Australia: Kate McCleary, Kye Grant, Alison Greenhalgh.

The Alfred Hospital, VIC, Australia: Scott Bradley, Jamie Cooper, Jasmin Board, Meredith Young, Emma Martin, Phoebe Mccracken, Claire Tipping.

The Prince Charles Hospital, Brisbane, QLD, Australia: Oystein Tronstad, Matthew Linnane, Lawrence Caruana.

The Royal Melbourne Hospital, VIC, Australia: Lisa Beach, Jane Larkin, Jenni Medland, Caitlin Devanny.

Toowoomba Hospital, QLD, Australia: Adam Visser, Courtney Campbell, Judy Smith, Corey Pendlebury, Georgia Staal.

Western Health Sunshine Hospital, VIC, Australia: Kimberley Haines, Lizzie Skinner, Irma Bilgrami, Elizabeth Hibbert, Jenna Lang, Nina Leggett, Melanie Paykel, Monica Voong, Sarah Burleigh, Kate Emery.

Wollongong Hospital, NSW, Australia: Martin Sterba, Wenli Geng, Nigel Thackeray.

New Zealand

Auckland City Hospital – CVICU, Auckland, New Zealand: Shay McGuiness, Racheal Parke, Pauline Tang, Eileen Gilder, Magdalena Butler, Keri-Anne Cowdrey, Karina Duffy, Samantha Ryan, Melissa Woollett, Patrick O'Kane, Laura Hughes, Marianne (Jane) Moore, Emma Sammon.

Auckland City Hospital – DCCM, Auckland, New Zealand: Colin McArthur, Caroline O'Connor, Yan Chen, Rachael McConnochie, Catherine Simmonds, Kane White.

Tauranga Hospital, Tauranga, New Zealand: Troy Browne, Jennifer Goodson, Tania Knight, Marko Kondov, Anna Stokes.

Waikato Hospital, Hamilton, New Zealand: Renesh Nair, Annette Forrest, Amelia Butler, Sarah Rogers, Livia Schischka, Kara Trask, Maree Zimmerman, Michelle Tonks.

Wellington Hospital, Wellington, New Zealand: Paul Young**,** Daniel Seller, Anna Hunt, Charlotte Latimer-Bell, Cassie Lawrence, Eden Lesona, Nina Lillo, Alexandra Millington, Leanlove Navarra, Shaanti Olatunji, Chelsea Robinson, April Aguilar, Raulle Cruz, Rhoze Sol Cruz, Kirsha Delaney, Harriet Judd, Yve Robinson, Nia Wyn Davies.

Ireland

Beacon Hospital, Dublin, Ireland – Daniel Collins, Michelle Smyth, Jane Dickenson.

St Vincent's Hospital, Dublin, Ireland: Alistair Nichol, Kathy Brickell, Máire Gilmartin, Michelle Smyth, Leanne Hayes, Enya Mulcahy, Michael O'Dwyer.

Tallaght University Hospital, Tallaght, Ireland: Arabella Fahy, Maria Baily-Scanlan, Sabina Mason, Elaine Joyce, Laura Hammond.

University Hospital Galway, Galway, Ireland: John Laffey, Siobhan Casey, Esther O Flaherty, Deirdre O'Dowd, Bairbre McNicholas, Maeve Kernan, Aoife Brenan, Claire Kelly, Ritika Ranjan.

Germany

Charité Universitätsmedizin Berlin, Germany: Stefan J Schaller, Annett Reißhauer, Julius Grunow, Friedrich Kuhn.

Klinikum rechts der Isar: **Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Munich, Germany**: Manfred Blobner, Stefan J Schaller, Kristina Fuest, Jana Schultz, Astrid Ruß.

Universitätsklinikum Leipzig, Leipzig, Germany: Sirak Petros, Kathrin Stöver, Simone Schwarz, Nadine Stegner, Frank Neubert, Niklas Hellwig, Christoph Schnabel.

United Kingdom

City Hospital, Nottingham University Hospitals, NHS Trust, UK: Martin Beed, Eleanor Douglas, Cecilia Peters, Lucy Ryan.

Frimley Park Hospital, Frimley, UK: George Evetts, Georgina Linstead, Hannah Boynes, Lianne Chapman.

Kings College Hospital NHS Foundation Trust, London, UK: Phil Hopkins, Emily Flowers, Rebecca Davies, Harriet Noble, Evita (Paris) Pappa, Maria Despante, Emma Clarey.

Morriston Hospital, Swansea Bay University Health Board, Wales, UK: Ceri Battle, Luke Newey, Sharon Storton.

Queen Elizabeth Hospital, Woolwich, Lewisham and Greenwhich NHS Foundation Trust, London, UK: Indu Karangoda**,** Rebecca Bays, Amy Collins, Estefania Trues.

Royal Cornwall Hospital, Royal Cornwall Hospitals NHS Foundation Trust, Truro, UK: William English, Alice Gibson, Michelle Hague, Sarah Bean, Karen Burt.

University Hospitals Lewisham, Lewisham and Greenwhich NHS Foundation Trust, London, UK: Waqas Khaliq, Harriet Bryce, Rosie Reece-Anthony.

Brazil

Hospital das Clínicas de Ribeirão Preto: Ada Clarice Gastaldi, Alessandra Fabiane Lago, Tiago Henrique Garcia da Silva, Larissa Perossi Nascimento

Instituto Hospital de Base Distrito Federal: Vinicius Maldaner, Renato Valduga, Juliana Alves, Barbara Alexandro, Michelle de Alexa.

Additional File 3

TEAM Outcome Assessors:

Australia

Liz Melgaard, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Amanda Brown, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Bentley Fulcher, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia.

New Zealand

Anne Turner, Medical Research Institute of New Zealand, Wellington, New Zealand

Ireland

Kathy Brickell, University College Dublin-Clinical Research Centre, St Vincent's Hospital, Dublin, Ireland.

Michelle Smyth, University College Dublin-Clinical Research Centre, St Vincent's Hospital, Dublin, Ireland.

Germany

Sarah Grotheer, Klinikum rechts der Isar: Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Munich, Germany.

Alicja Nowakowska, Klinikum rechts der Isar: Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Munich, Germany.

UK

Robert Darnell, Intensive Care National Audit and Research Centre, 14207, London, United Kingdom of Great Britain and Northern Ireland.

Brazil

Alessandra Lago, Hospital das Clinicas de Ribeirão Preto, São Paulo, Brazil.

Vinicius Maldaner, Instituto Hospital de Base Distrito Federal, Brasília, Brazil.

Appendix C. TEAM Data Safety and Monitoring Committee (DSMC)

DSMC chair

Prof Danny McAuley, The Royal Victoria Hospital and Queen's University of Belfast, Ireland.

DSMC members

Prof Catherine Hough, Oregon Health & Science University, Portland, Oregon, United States.

Prof David Harrison, Intensive Care National Audit and Research Centre, 14207, London, United Kingdom of Great Britain and Northern Ireland.

Trial Independent Statistician

Prof Michael Bailey, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia.

Appendix D. The TIDieR (Template for Intervention Description and Replication) Checklist*

	BRIEF NAME	
1.	Provide the name or a phrase that describes the intervention. Title - page 1	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention. Intervention -page 4 and ESM Appendix E	
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL). TEAM training video: https://youtu.be/9qKe44UVN	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities. Intervention -page 4 and ESM Appendix E.	
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given. Study population page 3 and ESM Appendix E..	
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group. Study population page 3 and ESM Appendix E.	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features. Study population page 3.	
	WHEN and HOW MUCH	
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	

Intervention pages 4-5, Figure 2 and ESM Appendix E.

TAILORING

9. If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.

Pages 4-5, Figure 2 and ESM Appendix E.

MODIFICATIONS

10.‡ If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).

Not applicable.

HOW WELL

11. Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.

Per protocol analyses page 11, ESM Appendix F.

12.‡ Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

Not applicable

Appendix E. Intervention of early activity and mobilisation

The intervention is identical to that successfully delivered in our multicentre pilot RCT. A mobility team comprising of a senior ICU physiotherapist (not the usual care physiotherapist in most instances), an allied health assistant and the ICU bedside nurse will complete all early activity & mobilisation interventions. Sites will be chosen on the basis of physiotherapist with education in both conducting and supervising patient activity and mobilisation as well as an understanding of ventilation.

Individually tailored, face to face delivery of the intervention will commence once the patient is randomised, in order to maximize early activity and muscle training.

Patients will be individually assessed daily for 7 days a week by an ICU physiotherapist face to face using the ICU Mobility Scale (IMS) to determine their highest level of mobility achieved. This reliable and valid scale ranges from 10 (walking independently) to zero (no active movement) and it was predictive of both discharge destination and 90 day survival in Australian survivors of prolonged IMV.

All efforts will be made to mobilise patients out of bed if the patient meet the physiological stability criteria as listed below:

- the absence of current brady-arrhythmia requiring pharmacological support
- a current ventricular rate ≤ 150 bpm and respiratory rate ≤ 45 bpm
- most recent lactate ≤ 4.0 mmol/L
- Current combined noradrenaline/adrenaline infusion rate of ≤ 0.2mcg/kg/min, OR if noradrenaline/adrenaline infusion rate has increased by more than 25% in the last 6hours, dose must be <0.1 mcg/kg/min.
- most recent cardiac index ≥ 2.0 L/min/m2 (where measured)
- current FiO2 ≤ 0.6 and PEEP ≤ 16 cm H2O
- not receiving NO, prone ventilation, neuromuscular blockers, prostacyclin, ECMO or HFOV

If the patient does not meet the criteria for out of bed early activity and mobilisation, the ICU medical and physio team will assess the safety of completing in-bed exercises (for example, reclined cycling, active strengthening exercises or active assisted exercises). If the patient is deemed too unstable for in-bed early activity then they will be re-assessed later in the day or early the following morning.

The IMS level will determine the dosage and type of active exercises the patient will receive, using the early activity and mobilisation protocol. This protocol is hierarchical, with the objective of each intervention session beginning with the highest level of activity possible for the longest time possible, which then steps down to lower levels of activity if the patient fatigues. Dose, duration and type of activity will be modified according to patient-related factors assessed on a daily basis.

Exercise intensity will be monitored using a visual card of the Borg Scale of rate of perceived exertion (category ratio 10), with a target of 3 to 5, which was previously shown to be reasonably safe and feasible. The intervention will be administered for the first 28 days from randomisation in the index ICU hospitalisation (i.e: any ICU day in the first 28 days from randomisation including re-admission to ICU within the first 28 days after randomisation), with data censored at day 180 after randomisation.

Appendix F. Data Collection Methods

Data will be collected on protocol adherence, including whether each intervention patient was assessed by a physiotherapist daily, the highest IMS ascertained, the duration of exercise at each level of the IMS and the total duration of active exercise during the intervention per day.

Protocol violations and adverse events / serious adverse events will be reported via the electronic database and evaluated by an independent medical monitor and the DSMC.

Patients (or a proxy – generally a close family member), who are alive at day 180 after randomisation, will be interviewed by the ANZIC-RC / MRINZ trained central assessor via telephone. If it is not possible for the patient or proxy to conduct the interview over the telephone, a copy of the relevant questionnaires will be sent to them via post. The trained assessor will administer, or the patient will complete the EQ5D5L, HADS, IES-R, WHODAS 2.0, ADL/IADL, and the MOCA-Blind questionnaires. Patients subsequently withdrawn for any reason or who did not receive their allocated study treatment will be followed up, according to the trial follow-up schedule, and analysed on an intention-to-tre

at principle.

Confidentiality of patient data

Patients will be randomised via a secure database and will be allocated a unique study number. The site research coordinator will compile an enrolment log including the patient's name, date of birth, hospital identification number, unique study number and date and time of randomisation. Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately. Follow up details of the patient and their person(s) responsible will be collected for the day 180 functional outcome assessment including name, address and contact telephone numbers and these contact details will be sent to central assessors.