Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work

Supplement to: Anderson CS, Arima H, Lavados P, et al. Cluster Crossover Trial of Head Positioning in Acute Stroke

Supplementary Appendix

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1. List of HeadPoST study group and trial investigators

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South America (Clinica Alemana de Santiago, Universidad del Desarrollo) - Pablo M Lavados, Paula Munoz-Venturelli, Francisca Gonzalez, Bernardita Portales, Octavio Pontes-Neto, Taiza Santos-Pontelli, Brunna Rimoli, and Monica Braga; *Centralised Follow-up* - Lorena Hoffmeister, Carolina Vidal, Dafna Benadof, Rodrigo J Rivas, Laura Carvallo, Pamela Carvallo, Rubia Miranda and Brunna Pileggi.

Sri Lanka (RemediumOne Pvt Ltd) - Shalomi Weerawardena, Thanushanthan Jeevarajah, Devaki Dharmawardena, Dumindi Ranasinghe, and Matheesha Dharshana; *Centralised Follow-up* – M M M Shafras, Nilesh Nandadeva, and Savithri Nawarathna.

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*United Kingdom (*Lancashire Clinical Trials Unit, University of Central Lancashire) - Caroline L Watkins, Gemma Whiteley, Denise Forshaw, Catherine Elizabeth Lightbody, Joanna Cox, Jane Fitzgerald, John F Heney, Helen Byfield, Simone Finley, and Hayley E Tyrer; *Centralised follow-up* - Carole Bruce, Alison Gibbon

Principal Investigators and Coordinators (according to country and hospital center, with numbers of patients in parentheses)

Australia (7 hospitals - 602 patients)

Calvary Public Hospital Bruce (179): Brett Jones, Emma Siracusa, Koushik Gowda, Shahla Cowans, Briana Forman, Sherin Jacob, Kristine Caprecho, Roshan Khatri, Po Yi Wan, Maria Lopez, Sifiso Vanika, Wilhelmina Bleeker and Marinka Ireland; *Royal North Shore Hospital (121):* Sheila Jala, Susan Day, Eric Ha, Martin Krause, Melissa Passer and Sarah Giaccari; *Royal Prince Alfred Hospital (133):* Nadia Burkolter, Michael Braithwaite and Kylie Tastula; *Concord Repatriation General Hospital (95): Fiona Stanley Hospital (39):* Darshan Ghia, Tapuwa Musuka, Anthony Alvaro, Gillian Edmonds and Nicole O'Loughin; Rebecca Phair and Joanne Kaoutal; *Sir Charles Gairdner Hospital (20):* David J.Blacker and Belinda L Saint; *Port Macquarie Base Hospital (15):* Kim Parrey, Michelle Coad, Matthew Kinchington, Nishantha Senanayake, Johanna Alaban and Irma Kuehne

Brazil (4 hospitals - 264 patients)

Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto - Universidade de Sao Paulo (HCFMRP-USP)(147): Taiza Santos-Pontelli, Monica Braga, Brunna Rimoli, Millene Camilo and Milena Libardi; *Clinicas de Porta Alegre (52):* Sheila Martins, Batista Carlos, Magda Martins, Leonardo Carbonera, Andrea Almeida and Martin Kelin; *Hospital Governador Celso Ramos(33):* Gladys Martins, Carla Pauli, Mariana Lunardi, Luciane Silveira, Olga Chagas and Daily Souza; *Hospital de Faculdade de Medicina de Botucatu- UNESP(32):* Rodrigo Bazan, Gabriel Braga, Priscila Ribeiro, Gustavo Luvizutto, Marcia Polin and Fernanda Winckler.

PR China (39 hospitals - 4479 patients)

Yangquan Coalmine Group General Hospital (155): Jinfeng Liu, Zhenjiang Wang, Huibing Wang, Suying Lin and Jing Dong; *Nanjing First Hospital, Nanjing Medical University (150):* Junshan Zhou, Suping Qin and Hui Zhan; *Dunhua City Hospital (144):* Yongquan Xue, Dong Tian, Dan Yang, Yan Yin and He Li; *85 Hospital of People's Liberation Army (142):* Changming Geng, Jieyi Liu, Xiaolin Jiang and Yujun Wu; *Third People's Hospital of Dalian (142):* Wei Sun; *Zhucheng Traditional Chinese Medicine Hospital (141):* Bingqi Yu, Yanmei Guan, Qin Wang, Bo Wei, Huirong Wang, and Yan Wang; *Hospital of Hebei Medical University (141):* Liwen Tai and Wenchao Zhang; *Affiliated Hospital of Chifeng University (141)*: Weili Zhao, Xueying Wang, Guoli Li, Zhiming Ni, Fudong Guo, Lan Cen, Jun Lu, Zheng Chen, Guoming Yin, Yingchun Wang, Jiping Zheng, Zhimin Zhou and Hongquan Wang; *The Third Hospital of Wafangdian (140):* Renlin Zou, Bin Xue, Airu Li, Jing Guo, Ying Guo and Xingguo Jiang; *Beijing Pinggu Hospital (140):* Xiuge Tan and Chunpeng Zhang; *The First Affiliated Hospital of Wenzhou Medical University (140):* Bei Shao and Xiaoting Niu; *The Second Affiliated Hospital of Soochow University (140):* Chunfeng Liu, Dongqin Chen, Ping Liang, Xia Zhang, Chunqing Zhang, Wenjie Gong, Zhichao Huang, Huihui Liu, Shoujiang You, Junying Huang and Rongfang Shi; *Qilu Hospital of Shandong University (140):* Cuilan Wang and Ying Liu; *Yutian County Hospital (138):* Jinchao Wang, Guojun Wu and Zhihong

Gao; *The Yongjia County People's Hospital (138):* Qunli Lin, Cong Xu, Huile Zheng, Xinghai Ye and Xiaoqiong Jin; *The Third Hospital of Hebei Medical University (133):* Junyan Liu, Xiaoyun Cao, Yan Zhang, Jinyang Wang, Yuzhu Xu and Yan Li; *Xuanwu Hospital Capital Medical University (132):* Xin Ma and Qi Kong; *Affiliated Hospital of Jining Medical University (131):* Yanlei Hao, Baojun Qiao and Hui Yan; *The Third People's Hospital of Huizhou (126):* Zhiyong Huang, Baoqiang Chang, Jinjin Yan, Pinjun Liao and Wei Zhang; *The People's Hospital of Nanpi County (124):* Ling Liu, Tingting Zhu, Xuehui Liu and Yongping Li; *The Second Cangzhou Central Hospital (121):* Ruifang Dong; *Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (121):* Miao Chen, Xiaoli Ge, Hairong Wang, Lihua Dai and Jiafu Liu; *Baogang Hospital (120):* Shixia Wang, Jihui Du and Aixiu Song; *Hospital Central South University (120):* Yunhai Li, Jie Feng and Cheng Yu; *The First Affiliated Hospital of Harbin Medical University (117):* Honglin Feng, Xiaojia Sun, Ruihong Sun, Weisong Liu and Jianfeng Liu; *People's Hospital of Hejian City (117): Tong Ren Hospital Shanghai Jiao Tong University School (117):* Xuesheng Lu and Enzhuo Chen; *Peking University Shougang Hospital (112):* Wei Gao, Hui Liu and Heping Wang; Yanxia Wang, Juan Song, Dongqi Liu, Wenhui Du, Guixia Li and Cuiling Li; *The Third Affiliated Hospital of Guangzhou Medical University (109):* Yanling Liang and Xuekun Cai; *The Chinese PLA No.263 Hospital (104):* Jinli Zhang and Xiaowei Tao; *Qinhuangdao Harbour Hospital (103)*: Pingshun An, Ranran Tang, Xu Qin, Yingling Wang and Wenjun Zhang; *Dongguan People's Hospital (101):* Rong Ma, Xiaoqiong Huang, Yonglin Liu and Yazhi Wang; *The Second Hospital of Nanchang (97)*: Ping Fan and Hailan Yang; *Bethune International Peace Hospital (85):* Lianyuan Feng and Jianxia Zhi; *XiangYa Xin Hua Henan Provincial People's Hospital (49):* Jiewen Zhang and Yao Zhou; *Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (46)*: Danhong Wu and Haiyan He; *The People's Hospital of Liaoning Province (42):* Xiaohong Chen; *Shijiazhuang Central Hospital (19):* Yongge Hou and Xiaohui Su; *Peking Union Medical College Hospital (1):* Liying Cui, Bin Peng and Siyuan Fan.

Chile (7 hospitals – 608 patients)

Hospital Base San José de Osorno (142): Luis Suárez, Juan de Dios Polanco, Patricio Sotomayor, Ricardo Urzúa, Daniela Urrutia, and Nathalie Conejan; *Hospital de Iquique Dr. Ernesto Torres Galdames (139):* Arturo Escobar, Monica Gonzalez, Danisa Vargas, Angel Constante, Erika Vásquez, and Elizabeth Godoy; *Complejo Asistencial Dr. Victor Ríos Ruíz de Los Angeles (114):* Christian Figueroa, Vanesa San Martin, Nataly Vidal, and Madeleyn Muñoz; *Clínica Alemana de Santiago (71):* Alejandro Brunser, María Spencer, Juan Almeida, and Ignacio Acosta; *Hospital Santiago Oriente Dr. Luis Tisné Brousse (64):* Rodrigo Guerrero, Prudencio Lozano, Camila Aguayo and Jimena Pizarro; *Hospital Regional Temuco Doctor Hernán Henríquez Aravena (64):* Alvaro Soto, Flor Bonilla, Pía García, Carolina Del Castillo, Marcela Grandjean and Alexis Von Johnn; *Hospital de Maipu El Carmen Dr Luis Valentin Ferrada (14):* Ignacio Gutierrez, Francisca Rivero, and Ignacio López.

Colombia (1 hospital – 38 patients)

Fundación Cardiovascular de Colombia, Bucaramanga (38): Federico Silva, Marlen Pachón, José Mendoza, and Alexander Pabón.

India (6 hospitals - 499 patients)

Christian Medical College and Hospital, Ludhiana (147): Mahesh Kate, Naushad Akhtar, Gibbsdeep S Narang and Ashish Deepak; *Mazumdar Shaw Medical Centre, a unit of Narayana Hrudayalaya Ltd, Bangalore (113):* Vikram Huded, Romnesh De Sowza, Alben Sigamani, Karthikeyan Rajendran, Anisha Vishwanath and Anusha K; *Dr. Ramesh Cardiac & Multispeciality Hosp. Pvt Ltd, Guntur (71):* Somasundaram Kumaravelu, Syed Rahamath and Sandeep Kannneganti; *Post Graduate Institute of Medical Education and Research, Chandigarh (64):* Dheeraj Khurana, Cheena Katoch and Taranpreet Kaur; *Baby Memorial Hospital Limited, Calicut (60):* Ummer Karadan, Anu Kuriakose, Jaison John and Mumthaz Basheer; *Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram (44):* Sylaja Padmavathy N and Sapna Erat Sreedharan.

Sri Lanka (4 hospitals – 271 patients)

Sri Jayawardenepura General Hospital (100): Harsha Hemal Gunasekara, Gamlath Chandima Udeni De Silva, Peetagam Harshi Lakmali Ubeywickrama, Kavisha Chathumali Silva and Eshani Anuradha De Silva; *Colombo North Teaching Hospital (92):* Udaya Ranawaka, Chamila Mettananda, Yamuna Nanayakkara, Tharini Mendis, Gayathri Fernando, Ahamed Imthikab and Kandula Pieris; *Colombo South Teaching Hospital (2 sites, 79):* Saman B Gunatilake, Pamuditha M W Madanayake, Shiran A Paranavitane, Bimsara Senanayake, Vaidhehi Vishwanathan, Maathury Sivapalan, Ruwangi U Murage, and Uthpala Chandradeva.

Taiwan (5 hospitals – 173 patients)

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United Kingdom (41 hospitals – 4160 patients)

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NHS Foundation Trust (76): Sue Potter, Rachel Gascoyne, Amanda Whileman, Emily Hall, Stephanie Wright, Julie Toms and Janet Tomlinson; *Luton and Dunstable University Hospital NHS Foundation Trust (75):* Lakshmanan Sekaran, Duke Phiri, Sakthivel Sethuraman, Niaz Mohammed, Frances Justin, Margaret Louise Tate and Meena Chauhan; *Countess of Chester Hospital NHS Foundation Trust (63):* Professor Kausik Chatterjee, Syed I Haider, Arumugam Nallasivan, Tim Webster, Sandra Leason and Samantha Seagrave; *Peterborough City Hospital, Peterborough and Stamford Hospitals NHS Foundation Trust (58):* Santhosh Subramonian, Peter Owksu-Agyei, Natalie Temple, Nicola Butterworth-Cowin and Frederick Magezi; *Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust (54):* Eleanor Turner, Shagufta Khan, Claire Stephens, Amit Mistri, Aidan Murphy, Manda Lam, Paul Underwood and Catherine Thompson; *Yeovil District Hospital NHS Foundation Trust (51):* Caroline Smith, Clare Buckley, Diane Wood, Sarah Board and Linda Howard; *Barnsley Hospital NHS Foundation Trust (51):* Sharon Johnson, Ashraf Ahmed and Bethany Oates; *Dorset County Hospital NHS Foundation Trust (50):* Damian F Jenkinson and Sara Leonard; *Royal Bournemouth Hospital, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust (46):* Becky J Jupp, Kamy Thavanesan, Michelle Dharmasiri, Sathyabama Logianathan, Catherine Ovington, Gail Hann and Chantel Cox; *Craigavon Area Hospital, Southern Health and Social care Trust, Northern Ireland (43):* Michael T McCormick, Catherine Douglas, Michael Goggin, Patricia Fearon, Sara Gilpin and Margaret O'Hagan; *Pilgrim Hospital, United Lincolnshire Hospitals NHS Trust (37):* David M Mangion, Anne Hardwick and Kimberley Netherton; *Bedford Hospital NHS Trust (21):* H Ni, Judith Quinn, Tulu Bozkaplan and Josin Jose.

2. Agencies providing funding for the study

The National Health and Medical Research Council (NHMRC) of Australia provided main funding through a research project grant (number 1066966). The other source of funding was from the Stroke Association of Brazil for conduct of the study in that country. The School of Health at the University of Central Lancashire, Preston, UK, provided considerable in-kind support for conduct of the study in the UK. These agencies had no role in the design of the trial protocol, in the collection, analysis, or interpretation of the trial data, or in the writing of the manuscript.

3. Screening procedures

Study personnel were required to maintain screening logs of all patients who presented with a definite or presumed acute stroke according to standard definitions during the study period. The number of patients listed on screening logs varied within and between countries depending on the referral patterns and status of hospitals. For the UK, participating hospitals included all patients in contact with stroke services, including patients referred from other hospitals for ongoing management rather than being the first hospital contact for acute treatment from ambulance dispatch in the community.

4. Hospital centers participating criteria and reasons for exclusion

The trial was planned to be conducted in up to 140 hospitals (centers) in Australia, Brazil, Chile, China, Mongolia, France, Taiwan, and the United Kingdom. Hospitals in other countries (such as Colombia, India and Sri Lanka) were invited to join according to interest, feasibility and resourcing. In the end, centers in Mongolia and France did not participate.

Centers were required to fulfill certain eligibility criteria, which included: having an established acute stroke care program with a geographically-defined area for the management of stroke patients (i.e. an acute stroke unit); having systems of care that enabled adherence to a specific head position policy; and having a sufficient projected throughput of patients to ensure feasibility of recruitment within a short study time frame. As such, there were some hospitals who recruited only a few patients as they entered late into the trial.

In total, 182 centers were approached and agreed to participate in the study. However, 68 failed to be participate for the reasons outlined below, by country.

Australia – the Principal Investigator at one center was unable to obtain approval from the multidisciplinary team on the acute stroke unit to participate in the study.

Brazil – the central government committee (CONEP) was slow in providing approval which led to delays in obtaining approvals from the local ethics committee of several centers within the study period.

Chile – the Principal Investigator at one center declined to participate due to limited resources.

China – the Principal Investigator of one center declined to participate due to limited resources, and the Principal Investigator at two other centers declined participation without reason after they had been activated to commence recruitment.

India – there was delay in obtaining approval from the central government (HMSC), which meant that several government hospitals could not participate within the study time period.

Sri Lanka – the Principal Investigator at one center changed his decision to participate due to concerns over the lying-flat position.

Taiwan – there were delays in obtaining ethics committee approvals at several centers, and one Principal Investigator could not obtain approval from his multidisciplinary stroke team to participate in the study

UK – hospitals were excluded due to lack of interest and delays in obtaining ethics committee approvals.

5. Patient participating inclusion/exclusion criteria

Patient inclusion criteria: All patients were eligible for the allocated intervention if at the time of presentation to hospital, if they had the following criteria:

1. aged ≥18 years;
2. a presumed clinical diagnosis of acute stroke (i.e. with a persistent neurological deficit on presentation);
3. either presented directly, transferred from another hospital, or had an in-hospital event.

Patient exclusion criteria: Patients were excluded from the allocated treatment if at the time of presentation they meet any of the following criteria:

1. had a transient ischemic attack (TIA) (i.e. brief neurological symptoms that are judged to have completely resolved upon presentation);
2. had a definite clinical indication or contraindication to either the sitting up or lying flat head positions;
3. had a significant medical condition that took priority in care and where adherence to the randomized head position was not possible on another ward/department of the hospital, for example for hemodialysis (e.g. chronic renal failure) or surgery (e.g. carotid endarterectomy, hematoma evacuation);
4. did not consent to participate in HeadPoST;
5. had previously enrolled in HeadPoST.

6. Consent process

Each participating center obtained written approval(s) from their Hospital Research Ethics Committee (EC) (e.g. Institutional Review Board [IRB]), and any other relevant regional or national bodies, before patient recruitment could commence. A mixed consent process was used, according to local/national rules and regulations. Consent was obtained under the cluster guardian format from an appropriate senior executive member of the center to apply the intervention as a standard of care. This was necessary to prevent contamination of the intervention across patients nursed in closed proximity and by busy clinicians caring for multiple patients. It was also used to avoid responder bias in patients (or surrogates) as a result of potentially thinking that they had received 'non-standard' care. Under the cluster guardian consent process, all eligible patients had received the intervention as standard of care. This was approved for the above reasons, and because the intervention was minimal risk and within the bounds of routine care and physiological boundaries. Next, patients were provided with an approved Patient Information Sheet (PIS) and Consent Form (CF) as soon as practical after admission for consent to collect their medical and personal information, and to contact them again for follow-up at 90 days. These patients in Australia, the process was an opt-out consent, where patients were required to formally opt-out of participating in the intervention and/or the outcome assessments.

7. Training of investigators

All HeadPoST investigators were trained in the protocol, Good Clinical Practice (GCP), and use of the National Institute of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) assessment scales if they had no recent certification.

8. Follow-up procedures for the 90-day assessment

Central office staff who were separate to those undertaking quality control monitoring of the study, undertook these assessments using the simplified mRS in all countries except Taiwan and India, where staff at centers undertook the 90-day assessments.

9. Implementation of the intervention and schedule for monitoring of sites

A statistician not otherwise involved in the trial, generated the randomized allocation sequence, stratified by country. This was concealed until the center was informed by the global project manager (J.L.) to commence the intervention. Centers were required to implement the first assigned randomized intervention position until an agreed target number of consecutive patients was reached, after which they crossed over to apply the other intervention to a similar number of consecutive patients.

A senior member of the clinical staff was a nominated champion at each center, to be responsible for ensuring education and training of clinical staff, and for monitoring implementation of the intervention.

Regionally-based research staff undertook initial training and quality control activities necessary for the conduct of the trial in accordance with the protocols, applicable guidelines and regulations. Monitoring visits following initiation and activation of the site took place if there were data irregularities or requested by investigators. All centers were monitored as a close out visit. Any significant deviation from the protocol was explained and documented in the protocol deviation/violation log and close-out monitoring visit report.

The close-out visit served to obtain verification of the following data for all patients randomized: patient consent forms (patient consent forms were reviewed for compliance with ICH GCP); patient existence; all outcome data; treatment allocation; and serious adverse event forms to source documents for 10% of all patients recruited at each center.

The study used a remote data monitoring process, whereby regional-based research staff submitted internet-based data reports on a weekly basis. A second data quality check was undertaken by the International Coordinating Center research staff on a monthly basis. Random statistical monitoring was also undertaken to check for data anomalies. Telephone contact was made to all centers before they were instructed to crossover to the second intervention.

At the end of the study, 114 centers had received at least one monitoring visit. A total of 129 monitoring visits were conducted: 90% were visited once, and 10% sites were visited twice.

10. Sample size and power calculations

The study was powered to determine a plausible, minimum clinically worthwhile, treatment effect in patients with acute ischemic stroke, where lowering the head of a patient from 30 ° to 15 ° or 0 °, has been associated with large, up to 11 cm/sec, increases in mean cerebral blood flow (CBF) in the middle cerebral artery on transcranial Doppler. Other studies have shown that a 1 cm/s increase in CBF is associated with a 0.7 point reduction in NIHSS score and 16% reduction in death or dependency on mRS, while the distribution of the mRS at 3 month follow-up in the sitting up head position has been reported to be 0 (18%), 1 (18%), 2 (16%), 3 (15%), 4 (12%), 5 (12%) and 6 (death, 9%). We estimated that the lying-flat head position would therefore produce a relative improvement of 16% (4% absolute) in functional outcome, as measured on the mRS at 90-days.

The power calculations were performed on the basis of a standard individual randomized trial with ordered categorical data methods,[1] and subsequently *inflated* by applying formulas developed for calculating the sample size requirement for cluster crossover trials.[2]

A sample size of 14,000 patients with acute ischemic stroke from 140 centres was estimated to provide 90% power (α 0.05) to detect ≥16% improvement (shift) in death and disability on the mRS at Day 90 in the ordinal logistic regression analysis, with the following assumptions:

- a cluster size of at least 60 patients with presumed acute ischemic stroke (50 true cases of acute ischemic stroke and another 10 cases of stroke mimics or poor implementation of head positioning in each intervention phase);
- 5% cross-over and 10% drop-out at each center;
- recruitment failure in 10%-15% of centers;
- an intra-cluster correlation (ICC) coefficient of 0.03; and
- no inter-period correlation (IPC).

This power calculation did not account for potential variability in effect sizes across centers.

This sample size would also provide 90% power to detect ≥16% improvement (shift) in death or neurological impairment on the NIHSS at Day 7, ≥30% reduction in death at Day 90, and ≥2 days reduction in hospital length of stay for patients with acute ischemic stroke.

We purposefully included patients with acute intracerebral hemorrhage. The cluster size to recruit consecutive patients with acute ischemic stroke would also include patients with acute intracerebral hemorrhage but these numbers were predicted to be smaller and variable across centers (10-30%), particularly between China and elsewhere, depending on the rates of intracerebral hemorrhage. The intention was to explore a treatment effect in patients with intracerebral hemorrhage, recognizing that the sample was under powered to assess modest effects. Assuming a recruitment of 10 such patients on average per center for each intervention period, a sample size of 2,800 patients with intracerebral hemorrhage from 140 sites was estimated to provide 90% power (α 0.05) to detect ≥25% improvement (shift) in death or disability associated with the sitting-up head position. Moreover, there would be 90% power to detect ≥25% in improvement in survival and NIHSS score at day 7, ≥33% decrease in death, and ≥2 days reduction in hospital length of stay for these patients.

Thus, the total planned sample size was 16,800 patients, which included 14,000 cases of acute ischemic stroke and 2,800 cases of intracerebral hemorrhage. The power of the trial was estimated conservatively and driven from having a large number of clusters, each of a feasible size that produced an achievable workload at each center. The inflation of the cluster size and the number of clusters was to take account of stroke mimics, poor recruitment and quality issues. *An overall target of patients in each cluster was 70 in each intervention was therefore derived from the requirement of 60 and 10 with acute ischemic stroke and acute intracerebral hemorrhage patients, respectively.*

The study ultimately ended up with 114 active centers and 9,736 patients with a primary outcome (mRS at 90-days), which equates to an average of 37 patients with acute ischemic stroke per cluster, per period. Given the completed study departed from the original assumptions in terms of the number and size of clusters, a review of the study power was warranted given the assumptions that had been made about ICC and IPC. Despite the

limitations of post-hoc power calculations,[3] our analyses indicate that the study retained an ability to assess the hypothesised difference (16% relative) for the achieved number of clusters, their variable size, and the observed degree of correlation within sites and within periods. The increase in ICC (0.085 vs 0.03) was more than compensated by there being an IPC 0.076 (the correlation between patients from the same cluster but from different periods) which had been conservatively assumed to be zero, which substantially increased power. *According to these numbers, the study maintained at least 90% power to detect a common odds ratio of 0.84, whilst maintaining the assumption of 5% of participants crossing over.*

11. Statistical analyses

Full details of the statistical analyses are outlined in the published statistical analysis plan. The NIHSS score at 7-days was categorized into 7 levels (<5, 5-9, 10-14, 15-19, 20-24, ≥25, and death), and analyzed using the same method as the shift analysis of the mRS score. Multiple imputation was performed with Fully Conditional Specification (FCS, i.e. chained equations) in PROC MI in SAS/STAT 14.1. Discriminant function method was used for categorical variables and linear regression for age of patient. We used 20 'burn-in' interactions for the FCS method for each of the 10 imputations. The results from the imputations were combined in PROC MIANALYZE.

The proportional odds assumption was checked using a plot of empirical logits by treatment group prior to the final analysis. The plot showed nearly parallel lines between treatment groups across all of the computed logits, which was taken as evidence that the proportional odds assumption was met.

We did not undertake any formal tests of model fit (e.g. deviance or Pearson Chi Square based on likelihood) because we used a pseudo-likelihood estimation method (subject specific residual likelihood method of Wolfringer and O'Connell,[4] which is incompatible with these goodness of fit tests.

For the unplanned analyses of adherence, BP levels and time in position were completed with hierarchical mixed models. We used the same random-effects structure as the main analysis. For permanent discontinuation of the randomized head position, we used a log link and binomial distribution (multi-level logistic regression), and for time spent in position and averaged BP level (summarised for each participant), we used an identity link and normal distribution (multi-level linear regression). The bands in Fig S1-S3 are 95% confidence intervals, calculated from individual level data (not taking into account clustering) from each measurement (4 hour intervals). We have not undertaken any formal tests of difference in lowest level of oxygen saturation.

The study did not use any multiplicity adjustment, but followed recommendations of Schulz and Grimes[5] by implementing the following steps: (i) clear pre-identification of all endpoints including the primary endpoint and the primary method of analysis; (ii) the protocol and pre-specified statistical analysis plan were made publically available; (iii) the results of all endpoints and pre-specified analyses are presented regardless of their statistical significance; and (iv) interpreting the results with moderation and in view of multiple comparisons.

12. Terms of reference of the Data Safety Monitoring Board (DSMB)

The DSMB was responsible for: safeguarding the interests of trial participants; assessing the safety and efficacy of the interventions during conduct of the trial; monitoring the overall conduct of the clinical trial; providing recommendations about stopping or continuing the trial to the Steering Committee; contributing to enhancing the integrity of the trial; formulating recommendations in relation to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMB was advisory to the Steering Committee. The Steering Committee was responsible for promptly reviewing the DSMB recommendations, deciding as to whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct were required. The DSMB were to conduct both periodical safety reviews and formal interim analyses. However, because of the short recruitment period, no formal interim analysis was undertaken. The DSMB undertook procedures according to the following: safety reviews which did not include formal testing of the efficacy data; dates of each DSMB meeting was made available to the unblinded statisticians with at least 6 weeks notice; the trial Principal Investigator, Co-Principal Investigators, and other members of the Trial Operations Committee, attended open sessions at the beginning of meetings, and were available at the end of meetings to answer any urgent questions; and the unblinded statisticians prepared the DSMB reports and attended the whole meeting to assist with interpretation of the results.

Safety reports were sent to the DSMB members on two occasions: the first meeting was held on 1 September 2015 after 997 patients were included; the other meeting was held on 18 April 2016 after 4500 patients had completed follow-up. The DSMB focussed on ensuring there was balanced recruitment of patients into each arm (based on screening logs; that is, there was not selection bias towards one of the head positions), and safety (based on reported SAEs and adherence to the head position). All meetings were held in-person and by teleconference.

For each DSMB meeting, Open and Closed Reports were provided. Open Reports, available to all who attended the DSMB meeting, include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up and compliance. Closed Reports, available only to those attending the Closed Sessions of the DSMB meeting, included analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of adverse events and symptom severity, and Open Report analyses that are displayed by intervention group.

The unblinded statistician(s) from The George Institute prepared both the open and closed reports. The Open and Closed Reports provided information that was accurate, with follow-up that was complete to within approximately one month of the date of the DSMB meeting. The Reports were provided to DSMB members 1-2 weeks prior to the date of the meeting.

Criteria for stopping or modifying the trial for safety were to be considered on the balance of ensuring safety for trial participants and how early stopping would impact on clinical practice. The Haybittle-Peto rule was used as a guide for proof beyond reasonable doubt in the monitoring of both efficacy and safety information in the trial. The DSMB worked on the principle that a difference of at least 3 standard deviations (SD) in an interim analysis of a major

outcome event (e.g. death from all causes or independent survival at 90 days) between patient groups would justify halting, or modifying, the study before the planned completion of recruitment. This criterion (Peto rule) has the practical advantage that the exact number of interim analyses is of less importance, and so no fixed schedule is proposed.

The DSMB did not advise the Steering Committee about the need to modify entry to the study (or seek extra data), and as such the Steering Committee, collaborators and central project staff remained ignorant of the interim results.

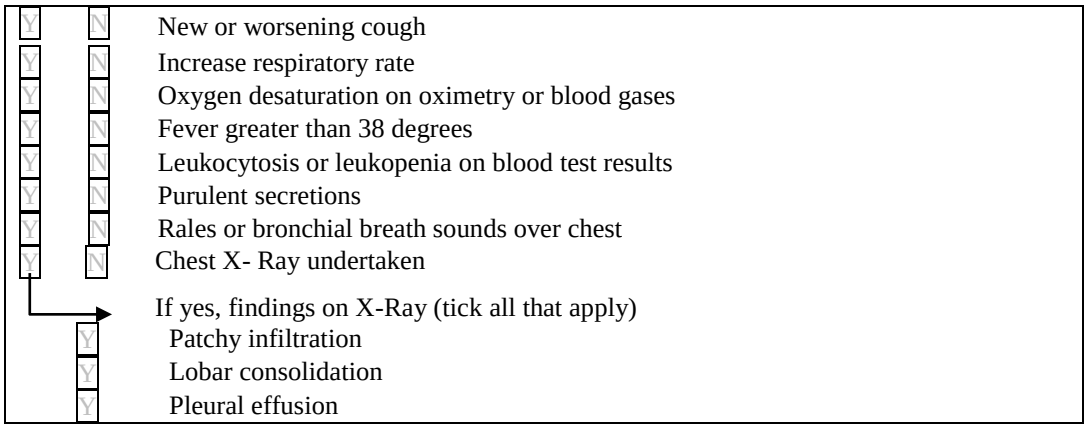
13. Recording of serious adverse events (SAEs)

The mechanisms for reporting, defining and notifying SAEs were based on the guidelines adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP). Full details were recorded for any SAE that was reported on a participant within the period of enrolment until the final assessment at 90 days. This included the potential relationship to the study procedures and protocol, and their management and outcome.

An SAE is defined as any untoward medical occurrence that:

- results in death;
- is life threatening in the opinion of the attending clinician;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- results in congenital anomaly or birth defect (NB females were likely post-menopausal);
- is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalization, but which may jeopardise the patient or may require intervention.

All SAEs were required to be reported to the ICC at The George Institute within 24 hours of the study team first becoming aware of the event by reporting the event in the electronic case record form (eCRF). SAEs were also required to be reported by the site investigator to the relevant EC / IRB in accordance with and within the timeframe specified in the relevant committee guidelines. An SAE of particular interest was pneumonia, defined as ‘definite’ and ‘probable’ according recent consensus criteria.[5] Any 3 or more of the features listed below: with any of the listed positive results of a chest x-ray was defined as ‘definite’, and any features without a chest x-ray or indefinite features on an x-ray, was defined as ‘probable’.



14. Tables

Table S1. Characteristics of hospitals

	Lying-flat/Sitting-up (N=57)	Sitting-up/Lying-flat (N=59)
Country – no. (%)		
Australia	2 (3.5)	5 (8.5)
Brazil	1 (1.8)	3 (5.1)
Chile	5 (8.8)	2 (3.4)
China	21 (36.8)	20 (33.9)
Colombia	1 (1.8)	0
India	3 (5.3)	3 (5.1)
Sri Lanka	1 (1.8)	3 (5.1)
Taiwan	2 (3.5)	3 (5.1)
UK	21 (36.8)	20 (33.9)
Public vs. private – no. (%)		
Public	54 (94.7)	56 (94.9)
Private	3 (5.3)	3 (5.1)
Location of hospital – no. (%)		
Metropolitan/urban	43 (75.4)	44 (74.6)
Semi-metropolitan/semi-urban	13 (22.8)	12 (20.3)
Rural/countryside	1 (1.8)	3 (5.1)
Teaching hospital – no. (%)		
Yes	47 (82.5)	49 (83.1)
No	8 (14.0)	10 (16.9)
Number of strokes per year – no. (%)		
<500	17 (29.8)	21 (35.6)
≥500	39 (68.4)	37 (62.7)

Table S2. Characteristics of all stroke patients at baseline, by treatment period

	Period 1		Period 2	
	Lying-flat (N=2845)	Sitting-up (N=3031)	Lying-flat (N=2450)	Sitting-up (N=2767)
Age - yr	68.0 ±14.0	68.3 ±13.8	67.5 ±13.8	67.9 ±13.6
Female sex – no. (%)	1183 (41.6)	1212 (40.0)	957 (39.1)	1077 (38.9)
Region of recruitment – no. (%)				
Australia/UK	1298 (45.6)	1350 (44.6)	916 (37.4)	1197 (43.3)
China/Taiwan	1187 (41.7)	1220 (40.3)	1024 (41.8)	1221 (44.1)
South America	259 (9.1)	195 (6.4)	202 (8.2)	254 (9.2)
India/Sri Lanka	101 (3.6)	266 (8.8%)	308 (12.6)	95 (3.4)
Medical history – no. (%)				
Hypertension	1448 (50.9)	1585 (52.3)	1263 (51.6)	1321 (47.7)
Any stroke	722 (25.4)	744 (24.5)	516 (21.1)	649 (23.4)
Coronary artery disease	394 (13.8)	469 (15.5)	296 (12.1)	380 (13.7)
Atrial fibrillation	334 (11.7)	323 (10.7)	221 (9.0)	298 (10.8)
Heart failure	91 (3.2)	142 (4.7)	75 (3.1)	104 (3.8)
Other heart disease	146 (5.1)	189 (6.2)	125 (5.1)	181 (6.5)
Diabetes mellitus	555 (19.5)	607 (20.0)	510 (20.8)	549 (19.8)
Hypercholesterolemia	615 (21.6)	666 (22.0)	498 (20.3	516 (18.6)
Tobacco use	543 (19.1)	576 (19.0)	444 (18.1)	561 (20.3)
No symptoms on the mRS before stroke†	1629 (57.3)	1898 (62.6)	1589 (64.9)	1628 (58.8)
Medications use – no. (%)				
Aspirin	1256 (44.1)	1249 (41.2)	1048 (42.8)	1245 (45.0)
Other antiplatelet agent	643 (22.6)	550 (18.1)	406 (16.6)	612 (22.1)
Anticoagulant	277 (9.7)	261 (8.6)	151 (6.2)	261 (9.4)
Systolic blood pressure - mmHg	156 ±28	155 ±28	154 ±27	156 ±28
Diastolic blood pressure - mmHg	87 ±17	86 ±17	87 ±16	87 ±17
NIHSS score‡	4.0 (2.0 9.0)	4.0 (2.0 9.0)	4.0 (2.0 8.0)	4.0 (2.0 8.0)
Time from stroke onset to intervention - hr	12.0 (5.0 29.0)	16.0 (6.0 42.0)	17.0 (6.0 42.0)	11.0 (5.0 29.0)
Time from hospital admission to intervention - hr	7.0 (2.0 24.0)	8.0 (2.0 29.0)	8.0 (2.0 29.0)	7.0 (2.0 25.0)
Swallow screen on admission – no. (%)	2223 (78.1)	2452 (80.9)	1993 (81.3)	2110 (76.3)
Swallow assessment on admission – no. (%)	1009 (35.5)	1190 (39.2)	835 (34.1)	880 (31.8)
Stroke type §				
Acute ischemic stroke	2377 (83.6)	2576 (85.0)	2147 (87.6)	2367 (85.5)
Intracerebral hemorrhage	243 (8.5)	277 (9.1)	176 (7.2)	234 (8.5)

*Data are means ±SD or median interquartile range. mRS denotes modified Rankin scale, NIHSS National Institutes of Health Stroke Scale,

†Scores on the mRS from 0 to 6, with higher scores indicating more severe disability

‡Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

§Reported by clinician investigator from brain imaging and other investigations on hospital discharge.

Table S3. Characteristics of stroke patients with acute ischemic stroke at baseline

Characteristic	Lying-flat (N = 4524)	Sitting-up (N = 4943)
Age - yr	68.0 ±13.8	68.5 ±13.5
Female sex - no. (%)†	1782 (39.4)	1937 (39.2)
Region of recruitment - no. (%)		
Australia/UK	1767 (39.1)	2065 (41.8)
China/Taiwan	1998 (44.2)	2180 (44.1)
South America	405 (9.0)	394 (8.0)
India/Sri Lanka	354 (7.8)	304 (6.2)
Medical history - no. (%)		
Hypertension	2307 (51.0)	2495 (50.5)
Any stroke	1060 (23.5)	1205 (24.3)
Coronary artery disease	589 (13.0)	747 (15.1)
Atrial fibrillation	499 (11.0)	562 (11.4)
Heart failure	148 (3.3)	209 (4.2)
Other heart disease	223 (4.9)	314 (6.4)
Diabetes mellitus	947 (20.9)	1030 (20.8)
Hypercholesterolemia	924 (20.4)	1004 (20.3)
Tobacco use	895 (19.8)	1028 (20.8)
No symptoms on the mRS before stroke†	2777 (61.4)	3012 (60.9)
Medication use – no. (%)		
Aspirin	2130 (47.1)	2323 (47.0)
Other antiplatelet agent	968 (21.4)	1080 (21.9)
Anticoagulant	363 (8.0)	459 (9.3)
Systolic blood pressure - mmHg	154 ±27	155 ±27
Diastolic blood pressure - mmHg	86 ±16	86 ±17
NIHSS score‡	4.0 (2.0-9.0)	4.0 (2.0-8.0)
Time from stroke onset to intervention - hr	15.0 (5.0-37.0)	14.0 (5.0-37.0)
Time from hospital admission to intervention - hr	8.0 (2.0-28.0)	8.0 (2.0-28.0)
Swallow screen on admission - no. (%)	3577 (79.1)	3888 (78.7)
Placed on restricted feeding regime - no. (%)	1610 (35.6)	1788 (36.2)

*Data are means ±SD or median interquartile range. mRS denotes modified Rankin scale, NIHSS National Institutes of Health Stroke Scale,

†Scores on the mRS from 0 to 6, with higher scores indicating more severe disability

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Table S4. Characteristics of stroke patients with intracerebral hemorrhage at baseline

Characteristic	Lying-flat (N = 419)	Sitting-up (N = 511)
Age - yr	67.0 ±13.9	65.3 ±14.0
Female sex - no. (%)†	183 (43.7)	202 (39.5)
Region of recruitment - no. (%)		
Australia/UK	162 (38.7)	202 (39.5)
China/Taiwan	180 (43.0)	222 (43.8)
South America	24 (5.7)	32 (6.3)
India/Sri Lanka	53 (12.6)	55 (10/8)
Medical history - no. (%)		
Hypertension	224 (53.5)	238 (46.6)
Any stroke	95 (22.7)	103 (20.2)
Coronary artery disease	34 (8.1)	51 (10.0)
Atrial fibrillation	29 (6.9)	27 (5.3)
Heart failure	6 (1.4)	14 (2.7)
Other heart disease	17 (4.1)	23 (4.5)
Diabetes mellitus	55 (13.1)	67 (13.1)
Hypercholesterolemia	58 (13.8)	71 (13.9)
Tobacco use	50 (11.9)	66 (12.9)
No symptoms on the modified Rankin scale before stroke†	239 (57.0)	306 (59.9)
Medication use – no. (%)		
Aspirin	47 (11.2)	67 (13.1)
Other antiplatelet agent	13 (3.1)	19 (3.7)
Anticoagulant	37 (8.8)	29 (5.7)
Systolic blood pressure - mmHg	167 ±31	165 ±30
Diastolic blood pressure - mmHg	92 ±18	92 ±19
NIHSS score‡	6.0 (2.0-12.0)	6.0 (2.5-12.0)
Time from stroke onset to intervention - hr	10.0 (4.0-28.0)	11.0 (4.0-29.0)
Time from hospital admission to intervention - hr	4.0 (2.0-22.0)	5.0 (2.0-24.0)
Swallow screen on admission - no. (%)	327 (78.0)	376 (73.6)
Placed on restricted feeding regime - no. (%)	152 (36.3)	189 (37.0)

*Data are means ±SD or median interquartile range. mRS denotes modified Rankin scale, NIHSS National Institutes of Health Stroke Scale,

†Scores on the mRS from 0 to 6, with higher scores indicating more severe disability

‡Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

Table S5. Adherence to allocated head position and oxygen saturation levels*

	Lying-flat (N=5295)	Sitting-up (N=5798)	OR/MD (95% CI)	P value
Time spent in allocated position - hr				
N	N=5191	N=5759		
Mean ±SD	20.9 ±5.2	22.5 ±3.3		
Median (iqr)	23.3 (20.0-24.0)	24.0 (23.0-24.0)	-1.6 (-2.1 to -1.2)	<0.0001
Min, max	0.33, 24.00	1.00, 24.00		
Lowest oxygen saturation (%)				
N	N=3810	N=4258		
Mean, SD	95.3 ±2.5	95.3 ±3.0		
Median (iqr)	95.0 (94.0-97.0)	95.0 (94.0-97.0)		
Min, Max	68.00, 100.0	9.00, 100.0		
Intervention discontinued permanently - n (%)				
No	4578 (86.5)	5529 (95.4)	4.0 (3.1 to 5.3)	<0.0001
Yes	695 (13.1)	245 (4.2)		
Reason for discontinuation	-	-		
Not tolerated	201 (28.9)	21 (8.6)		
Unable to comply	73 (10.5)	11 (4.5)		
Patient preference	135 (19.4)	37 (15.1)		
Doctor preference	35 (5.0)	5 (2.0)		
Change in medical condition	85 (12.2)	11 (4.5)		
Other	166 (23.9)	158 (64.5)		
Not specified	-	2 (0.8)		

*Data are means ±SD or median interquartile range. CI denotes confidence interval, MD mean difference, OR odds ratio

Hierarchical mixed models were used for analyses of adherence and time in position. The same random-effects structure was used as in the main analysis. For permanent discontinuation of the randomized head position, a log link and binomial distribution (multi-level logistic regression) was used, and for time spent in position, an identity link and normal distribution (multi-level linear regression) was used. No formal tests of difference in lowest level of oxygen saturation was undertaken.

Table S6. Interventions delivered during the 24-hour interventional head positioning period and over next 6 days in hospital.

Intervention	Lying-flat (N=5295) n\N (%)	Sitting-up (N=5798) n\N (%)
Aspirin	4102/5269 (77.9)	4361/5769 (75.6)
Other antiplatelet agent	1950/5261 (37.1)	2083/5766 (36.1)
Intravenous alteplase or other lytic agent	655/5293 (12.4)	667/5790 (11.5)
Endovascular clot retrieval	68/5274 (1.3)	35/5777 (0.6)
Decompressive hemicranectomy	12/5274 (0.2)	11/5778 (0.2)
Intensive blood pressure lowering	443/5293 (8.4)	477/5790 (8.2)
Oral anticoagulant therapy	364/5271 (6.9)	434/5762 (7.5)
Subcutaneous unfractionated heparin	920/5268 (17.5)	978/5766 (17.0)
Antibiotic treatment	803/5264 (15.3)	879/5776 (15.2)
Intravenous mannitol	478/5262 (9.1)	495/5765 (8.6)
Statins	4042/5261 (76.8)	4450/5764 (77.2)
Antihypertensive agent(s)	3067/5262 (58.3)	3381/5766 (58.6)
Intensive care unit admission	254/5257 (4.8)	263/5767 (4.6)
Acute stroke unit/ward admission	3135/5294 (59.2)	3475/5782 (60.1)
Intermittent pneumatic calf compression	799/5245 (15.2)	699/5747 (12.2)
Physiotherapy received	3011/5256 (57.3)	3349/5777 (58.0)
Occupational therapy received	2087/5262 (39.7)	2368/5767 (41.1)
Intravenous traditional Chinese medicine(s)	1096/5264 (20.8)	1358/5770 (23.5)
Intravenous neuroprotective agent(s)	1535/5264 (29.2)	1716/5764 (29.8)

Table S7. Source of information on the modified Rankin Scale in patients who were assessed at 90 days

Assessment type	Randomized head position		Total
	Lying-flat N=4676 n (%)	Sitting-up N=5072 n (%)	9748 n (%)
Face to face	31 (0.7)	36 (0.7)	67 (0.7)
Other/uncoded	552 (11.8)	631 (12.4)	1183 (12.1)
Phone to caregiver	2296 (49.1)	2451 (48.3)	4747 (48.7)
Phone to patient	1796 (38.4)	1951 (38.4)	3747 (38.4)
Phone to patient's doctor	1 (-)	3 (-)	4 (-)

Table S8. Main outcomes for patients with acute ischemic stroke*

Outcome	Lying-flat	Sitting-up	OR (95% CI) MD (95% CI)	P value
Primary - mRS at Day 90	N=4027	N=4356		
Ordinal analysis – no. (%)				
0 (no symptoms)	603 (15.0)	773 (17.7)	1.03 (0.94 to 1.13)	0.52†
1 (no significant disability)	1500 (37.3)	1481 (34.0)	1.08 (0.97 to 1.19)	0.15‡
2 (slight disability)	365 (9.1)	390 (9.0)	1.05 (0.95 to 1.16)	0.35 §
3 (moderate disability)	617 (15.3)	701 (16.1)	1.05 (0.95 to 1.16)	0.36 ¶
4 (moderate/severe disability)	386 (9.6)	384 (8.8)		
5 (severe disability)	247 (6.1)	284 (6.5)		
6 (dead)	309 (7.7)	343 (7.9)		
Death or disability - no. (%)				
mRS scores 0-2 (favourable)	2468 (61.3)	2644 (60.7)	0.96 (0.86 to 1.07)	0.49†
mRS scores 3-6 (poor)	1559 (38.7)	1712 (39.3)		
Vital status at Day 90	N=4437	N=4834		
Alive	4118 (93.0)	4481 (92.9)	1.00 (0.85 to 1.18)	0.99†
Dead	309 (7.0)	343 (7.1)		
MRS at Day 7 - no. (%)	N=4490	N=4905		
Ordinal analysis				
0 (no symptoms)	639 (14.2)	714 (14.6)	1.06 (0.95 to 1.17)	0.29†
1 (no significant disability)	1215 (27.1)	1421 (29.0)		
2 (slight disability)	907 (20.2)	970 (19.8)		
3 (moderate disability)	622 (13.9)	646 (13.2)		
4 (moderate/severe disability)	662 (14.7)	697 (14.2)		
5 (severe disability)	386 (8.6)	398 (8.1)		
6 (dead)	59 (1.3)	59 (1.2)		
NIHSS at Day 7 – no. (%)‖	N=4380	N=4803		
Ordinal analysis				
1 (<5)	2969 (67.8)	3296 (68.6)	1.01 (0.91 to 1.11)	0.89†
2 (5-9)	722 (16.5)	775 (16.1)	1.03 (0.93 to 1.14)	0.56‡
3 (10-14)	354 (8.1)	372 (7.7)	0.98 (0.88 to 1.10)	0.77 §
4 (15-19)	151 (3.4)	172 (3.6)	0.98 (0.89 to 1.09)	0.77 ¶
5 (20-24)	89 (2.0)	78 (1.6)		
6 (≥25)	36 (0.8)	51 (1.1)		
7 (dead)	59 (1.3)	59 (1.2)		
Continuous analysis	4.4±5.4	4.4±5.4	-0.09 (-0.3 to 0.2)	0.48†

*Plus-minus values are means±SD. CI denotes confidence interval, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, OR odds ratio, MD mean difference.

†Modelled using a hierarchical linear mixed model with a fixed group effect, a fixed period effect, a random cluster effect and a random cluster-period effect.

‡Adjusted analysis includes covariates of country, pre-stroke mRS score, age and sex

§Second adjusted analysis includes the additional covariates of baseline NIHSS score, and history of heart disease, stroke or diabetes mellitus.

¶Imputed analysis.

‖Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

Table S9. Main outcomes for patients with intracerebral hemorrhage*

Outcome	Lying-flat	Sitting-up	OR (95% CI) MD (95% CI)	P value
Primary - mRS at Day 90	N=374	N=445		
Ordinal analysis – no. (%)				
0 (no symptoms)	47 (12.6)	62 (13.9)	0.99 (0.71 to 1.39)	0.97†
1 (no significant disability)	118 (31.6)	140 (31.5)	0.99 (0.72 to 1.34)	0.93‡
2 (slight disability)	25 (6.7)	23 (5.2)	0.95 (0.71 to 1.27)	0.73 §
3 (moderate disability)	57 (15.2)	75 (16.9)	1.02 (0.78 to 1.33)	0.90 ¶
4 (moderate/severe disability)	43 (11.5)	51 (11.5)		
5 (severe disability)	30 (8.0)	36 (8.1)		
6 (dead)	54 (14.4)	58 (13.0)		
Death or disability – no. (%)				
mRS scores 0-2 (favourable)	190 (50.8)	225 (50.6)	0.92 (0.65 to 1.31)	0.66†
mRS scores 3-6 (poor)	184 (49.2)	220 (49.4)		
Vital status at Day 90	N=409	N=506		
Alive	355 (86.8)	448 (88.5)	1.07 (0.66 to 1.73)	0.78†
Dead	54 (13.2)	58 (11.5)		
MRS at Day 7 – no. (%)	N=418	N=502		
Ordinal analysis				
0 (no symptoms)	52 (12.4)	55 (11.0%)	1.07 (0.79 to 1.45)	0.67†
1 (no significant disability)	87 (20.8)	112 (22.3%)		
2 (slight disability)	55 (13.2)	84 (16.7%)		
3 (moderate disability)	58 (13.9)	64 (12.7%)		
4 (moderate/severe disability)	84 (20.1)	83 (16.5%)		
5 (severe disability)	67 (16.0)	88 (17.5%)		
6 (dead)	15 (3.6)	16 (3.2%)		
NIHSS at Day 7 – no. (%)‖	N=410	N=487		
Ordinal analysis				
1 (<5)	219 (53.4)	261 (53.6)	1.04 (0.75 to 1.44)	0.82†
2 (5-9)	77 (18.8)	92 (18.9)	1.04 (0.74 to 1.47)	0.81‡
3 (10-14)	54 (13.2)	58 (11.9)	0.95 (0.67 to 1.34)	0.77 §
4 (15-19)	22 (5.4)	34 (7.0)	0.93 (0.68 to 1.29)	0.68 ¶
5 (20-24)	14 (3.4)	15 (3.1)		
6 (≥25)	9 (2.2)	11 (2.3)		
7 (dead)	15 (3.7)	16 (3.3)		
Continuous analysis	6.1 ±6.7	6.3 ±6.9	-0.10 (-1.2 to 1.0)	0.85†

*Plus-minus values are means ±SD. CI denotes confidence interval, mRS modified Rankin scale, MD mean difference, NIHSS National Institutes of Health Stroke Scale, OR odds ratio.

†Modelled using a hierarchical linear mixed model with a fixed group effect, a fixed period effect, a random cluster effect and a random cluster-period effect.

‡Adjusted analysis includes covariates of country, pre-stroke mRS score, age and sex

§Second adjusted analysis includes the additional covariates of baseline NIHSS score, and history of heart disease, stroke or diabetes mellitus.

¶Imputed analysis.

‖Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

Table S10. Analysis of time to death and time to hospital separation

Outcome	Lying-flat (N=5295)	Sitting-up (N=5798)	Hazard Ratio	P value*
Time to death	Not Estimable	Not Estimable	1.01 (0.86 - 1.17)	0.93
Time to hospital discharge	9 (4-15)	9 (4-15)	0.99 (0.94 - 1.04)	0.68

*****calculations based on this reference: Lin DY, Wei LJ. The robust inference for the Cox proportional hazard model. J Am Stat Assoc 1989; 84: 1074-1078.

Table S11. Health-related quality of life according to the EQ-5D at 90 days

EQ5D		Lying-flat (N=5295) n (%)		Sitting-up (N=5798) n (%)	OR (95% CI) / MD (95% CI)	P value
Mobility		N=4289		N=4654	1.00 (0.90 to 1.11)	0.99
I have no problems in walking about		2570 (59.9)		2793 (60.0)		
I have some problems in walking about		1345 (31.4)		1440 (30.9)		
I am confined to bed		374 (8.7)		421 (9.0)		
Self-care		N=4291		N=4653	0.97 (0.88 to 1.08)	0.59
I have no problems with self-care		2843 (66.3)		3082 (66.2)		
I have some problems washing or dressing myself		920 (21.4)		980 (21.1)		
I am unable to wash or dress myself		528 (12.3)		591 (12.7)		
Usual activities		N=4292		N=4653	0.93 (0.83 to 1.04)	0.21
I have no problems with performing my usual activities		2249 (52.4)		2388 (51.3)		
I have some problems with performing my usual activities		1376 (32.1)		1497 (32.2)		
I am unable to perform my usual activities		667 (15.5)		768 (16.5)		
Pain/discomfort		N=4286		N=4644	0.95 (0.84 to 1.07)	0.36
I have no pain or discomfort		2920 (68.1)		3131 (67.4)		
I have moderate pain or discomfort		1175 (27.4)		1310 (28.2)		
I have extreme pain or discomfort		191 (4.5)		203 (4.4)		
Anxiety/Depression		N=4281		N=4643	1.02 (0.89 to 1.16)	0.81
I am not anxious or depressed		3082 (72.0)		3375 (72.7)		
I am moderately anxious or depressed		991 (23.1)		1037 (22.3)		
I am extremely anxious or depressed		208 (4.9)		231 (5.0)		
Overall health state	4246	72.9 ±19.8	4584	71.6 ±20.5	-1.4 (-0.4 to -2.4)	0.009

*Plus-minus values are means ±SD. CI denotes confidence interval, MD mean difference, OR odds ratio

Table S12. Safety outcomes – serious adverse events (SAEs)

	Lying-flat (N=5295)		Sitting-up (N=5798)		
	#events[1]	n (%)[2]	#events[1]	n (%)[2]	P value[3]
All SAEs	922	756 (14.3)	952	784 (13.5)	0.51
Cardiovascular	422	409 (7.7)	439	414 (7.1)	0.23
Acute stroke	299	284 (5.4)	304	295 (5.1)	0.44
Cardiac	50	49 (0.9)	41	40 (0.7)	0.12
Other vascular	93	90 (1.7)	94	91 (1.6)	0.38
Non-cardiovascular	439	364 (6.9)	474	405 (7.0)	0.43
Pneumonia	178	164 (3.1)	214	198 (3.4)	0.52
Other infection	77	72 (1.4)	92	85 (1.5)	0.78
Other	184	164 (3.1)	168	156 (2.7)	0.36
Unclassified	41	40 (0.8)	39	38 (0.7)	0.66
Fatal SAEs	281	278 (5.3)	315	311 (5.4)	0.38
Cardiovascular	175	174 (3.3)	195	195 (3.4)	0.85
Acute stroke	134	134 (2.5)	141	141 (2.4)	0.78
Cardiac	10	10 (0.2)	17	17 (0.3)	0.42
Other vascular	31	31 (0.6)	37	37 (0.6)	0.34
Non-cardiovascular	68	67 (1.3)	83	81 (1.4)	0.83
Pneumonia	40	39 (0.7)	46	45 (0.8)	0.77
Other infection	7	7 (0.1)	12	12 (0.2)	0.44
Other	21	21 (0.4)	25	25 (0.4)	0.26
Unclassified	36	35 (0.7)	33	32 (0.6)	0.36

[1]Total number of events (one patient can contribute more than one event)

[2]Proportion of patients with at least one event

[3]P-value from cluster-period level analysis using linear regression

Table S13. Frequency of pneumonia by standardized criteria*

Pneumonia diagnosis	Lying-flat N (%)	Sitting-up N (%)	P value†
Definite	31 (17.4)	29 (13.6)	0.56
Probable	10 (5.6)	14 (6.5)	.
Uncertain	137 (77.0)	171 (79.9)	.

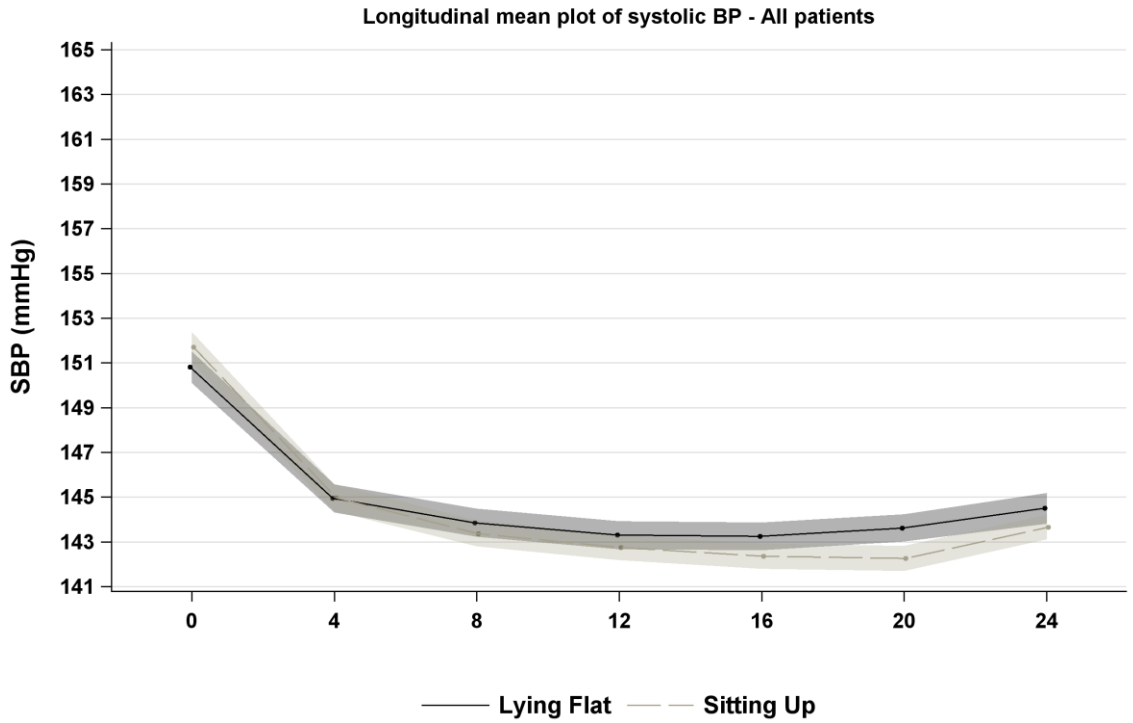
*Definite pneumonia defined as ≥3 of the following symptoms (new/worsening cough, increased respiratory rate, oxygen desaturation, fever [>38 ℃], leucocytosis or leukopenia, purulent secretions, and rales or bronchial breath sounds over the chest) *plus* a chest X-ray indicating any of patchy infiltration, lobar consolidation or pleural effusion; probable pneumonia is ≥3 of the symptoms above *without* a chest X-ray or chest X-ray indicating the features above; and uncertain pneumonia is <3 symptoms with/without chest X-ray

†P value is a test of whether type of diagnosis differs by group, estimated with nominal logistic regression with Morel variance adjustment for clustering

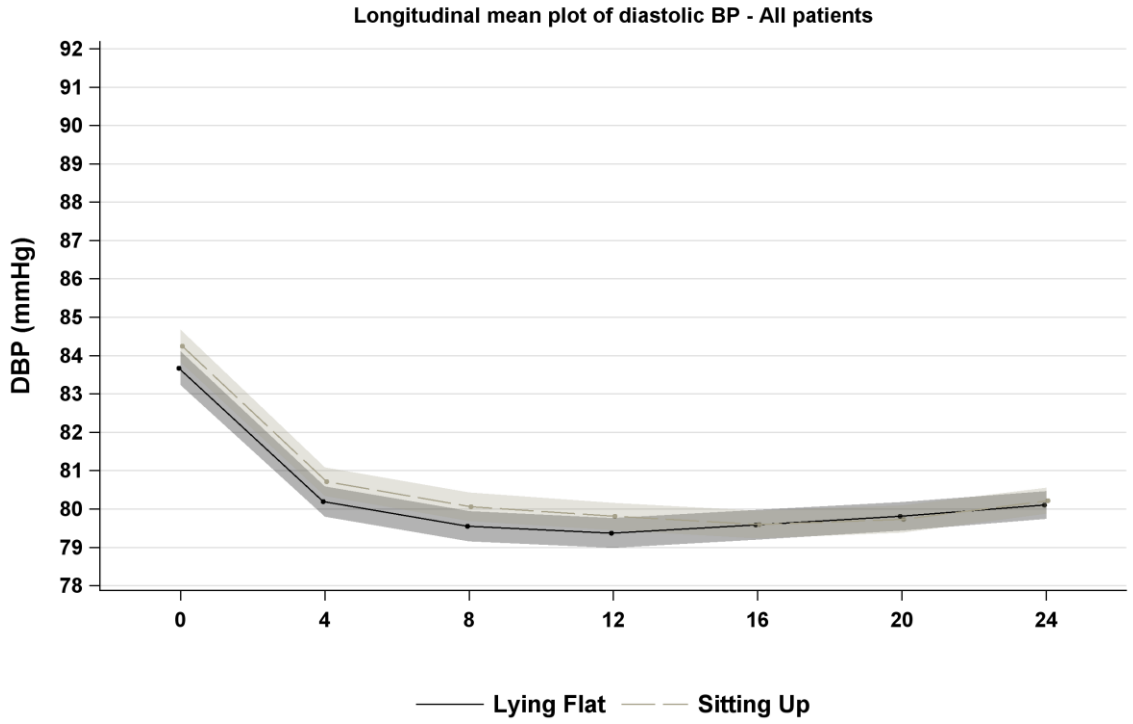
15. Figures

Figure S1. Systolic and diastolic blood pressure (BP) levels over 24 hours in all patients*

Mean difference in average systolic BP -0.29 (95% CI -0.49 - 1.07) P=0.47

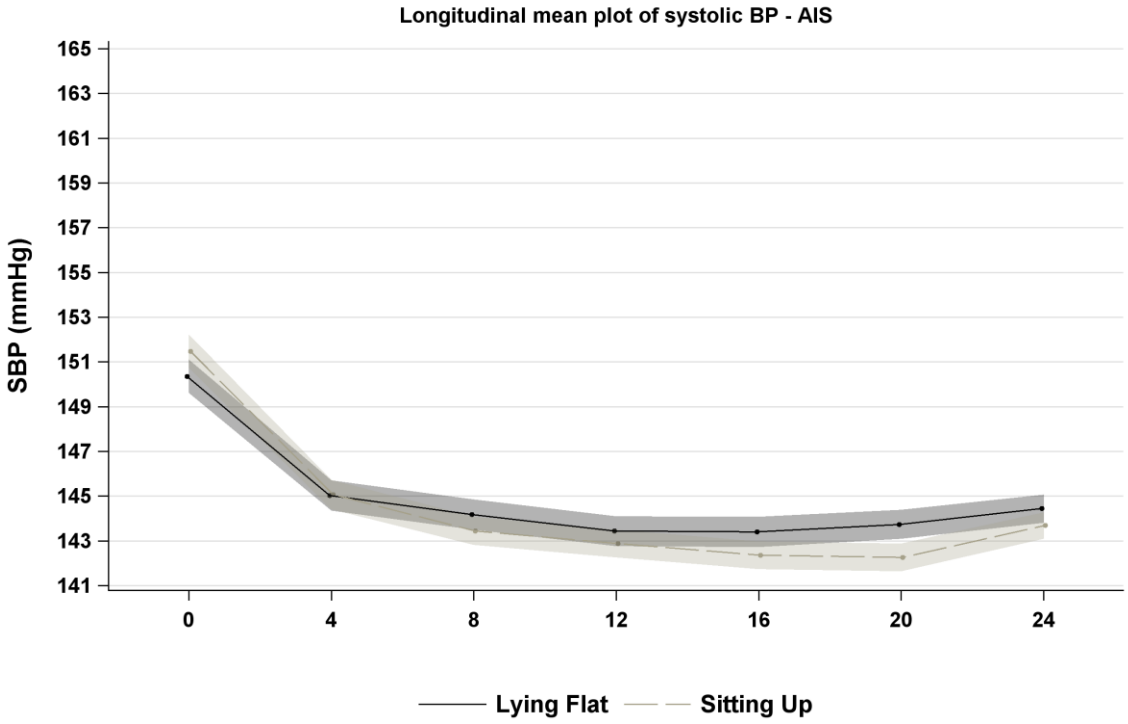


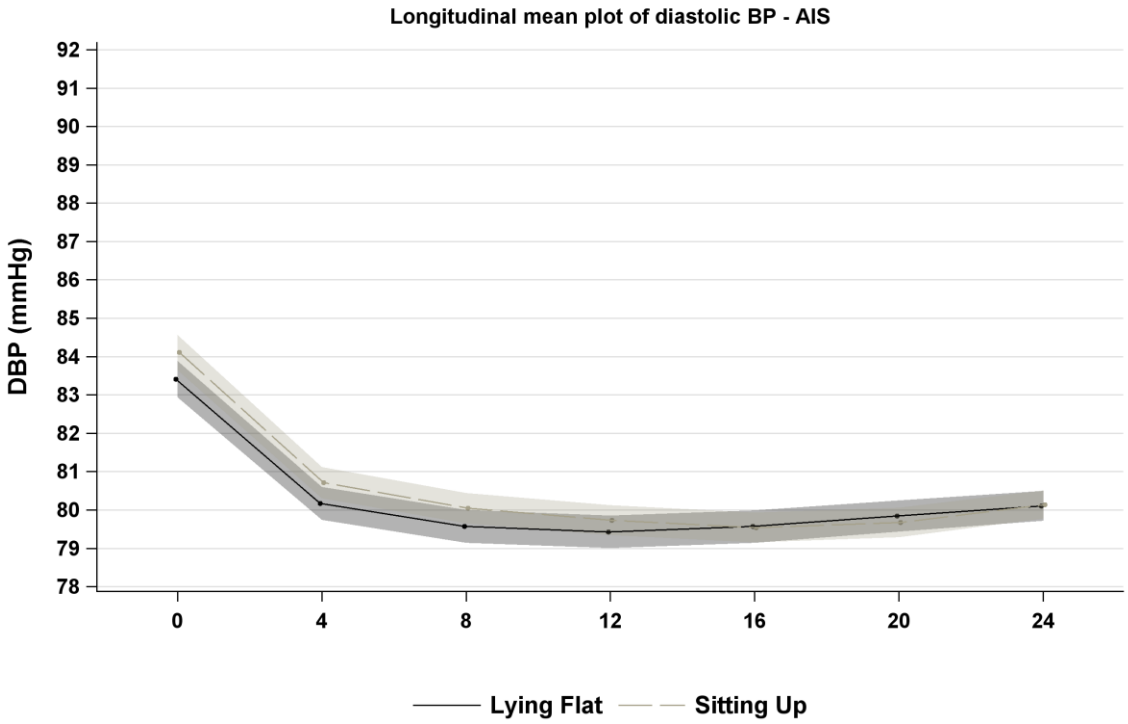
Mean difference in average diastolic BP 0.41 (95%CI -0.91 - 0.15) P=0.15



*For these unplanned analyses, similar random-effects structure were used for the main analysis. Averaged BP level (summarised for each participant) were estimated using an identity link and normal distribution (multi-level linear regression). The bands represent 95% confidence intervals (CI), calculated from individual level data (not taking into account clustering) from each measurement (4 hour intervals).

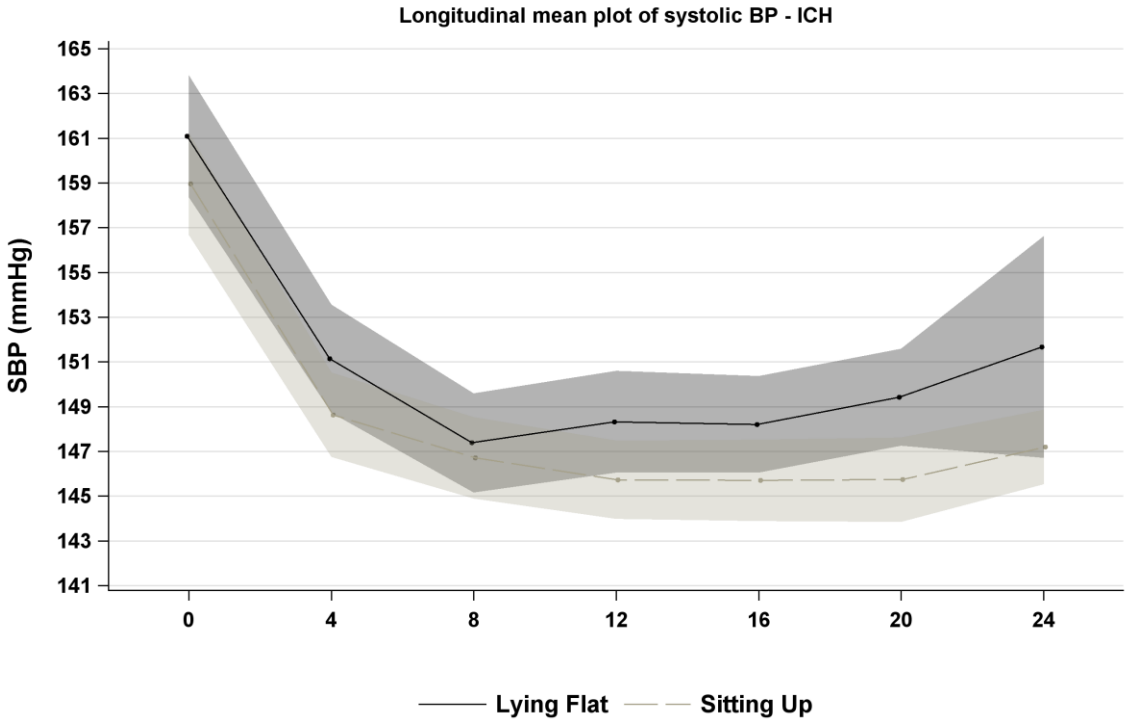
Figure S2. Systolic and diastolic blood pressure (BP) levels over 24 hours in patients with acute ischemic stroke*

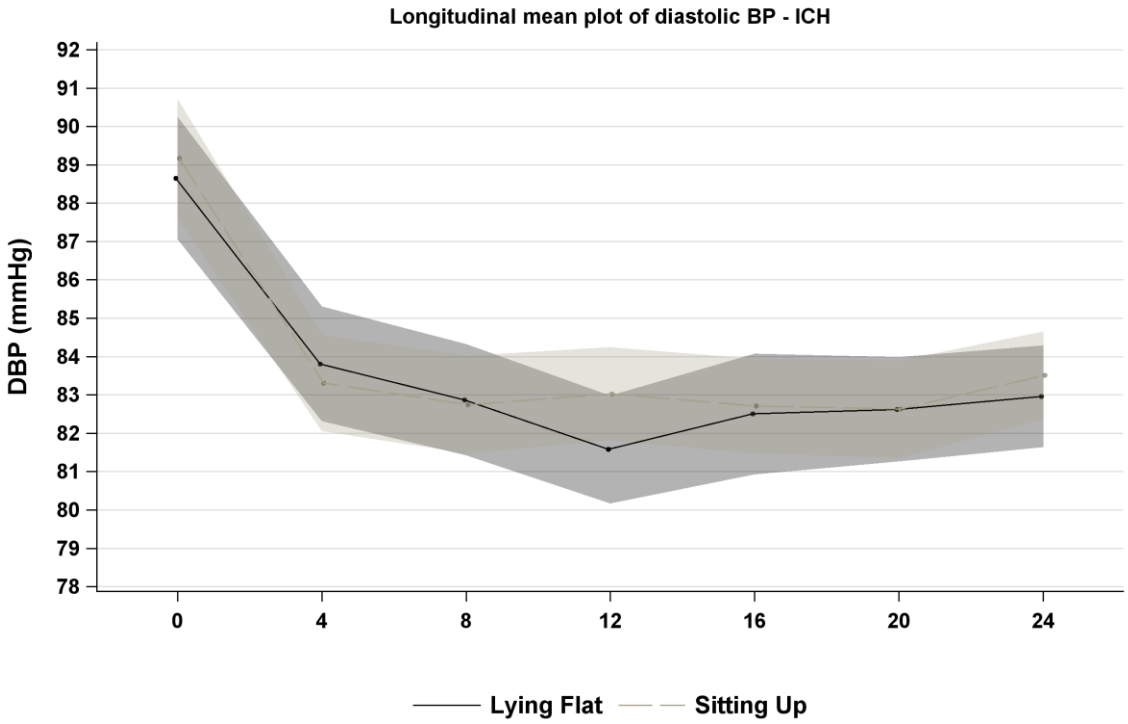




*For these unplanned analyses, similar random-effects structure were used for the main analysis. Averaged BP level (summarised for each participant) were estimated using an identity link and normal distribution (multi-level linear regression). The bands represent 95% confidence intervals (CI), calculated from individual level data (not taking into account clustering) from each measurement (4 hour intervals).

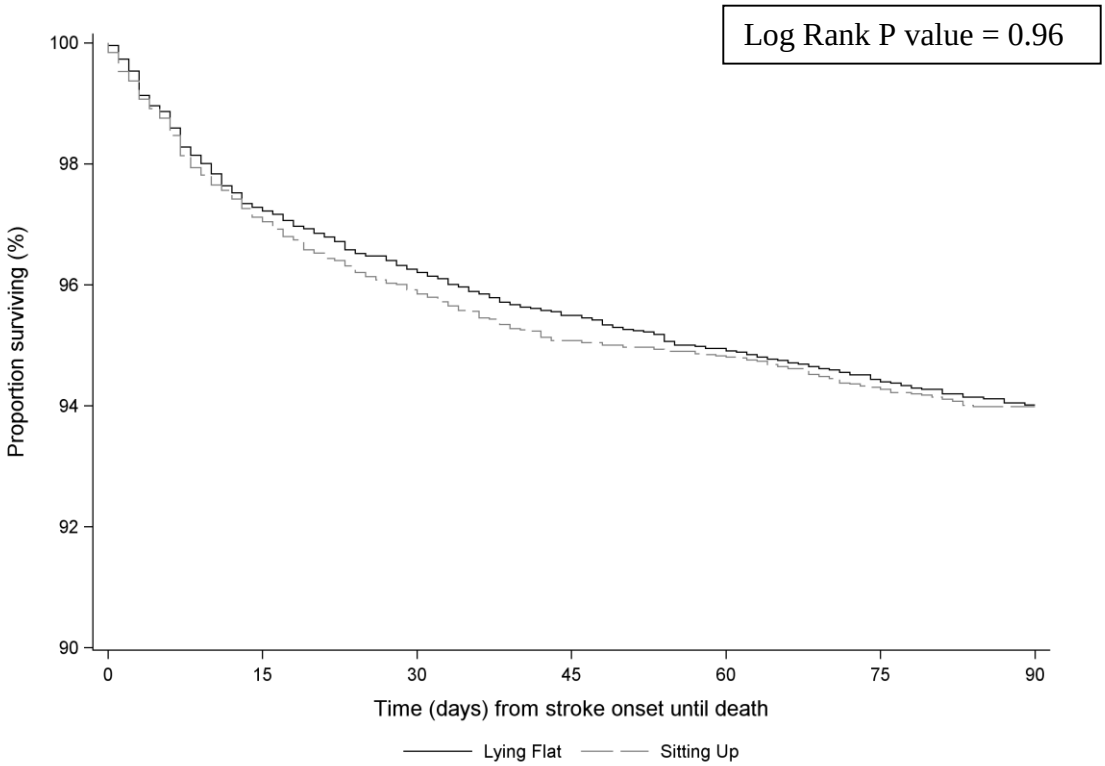
Figure S3. Systolic and diastolic blood pressure (BP) levels over 24 hours in patients with intracerebral haemorrhage*





*For these unplanned analyses, similar random-effects structure were used for the main analysis. Averaged BP level (summarised for each participant) were estimated using an identity link and normal distribution (multi-level linear regression). The bands represent 95% confidence intervals (CI), calculated from individual level data (not taking into account clustering) from each measurement (4 hour intervals).

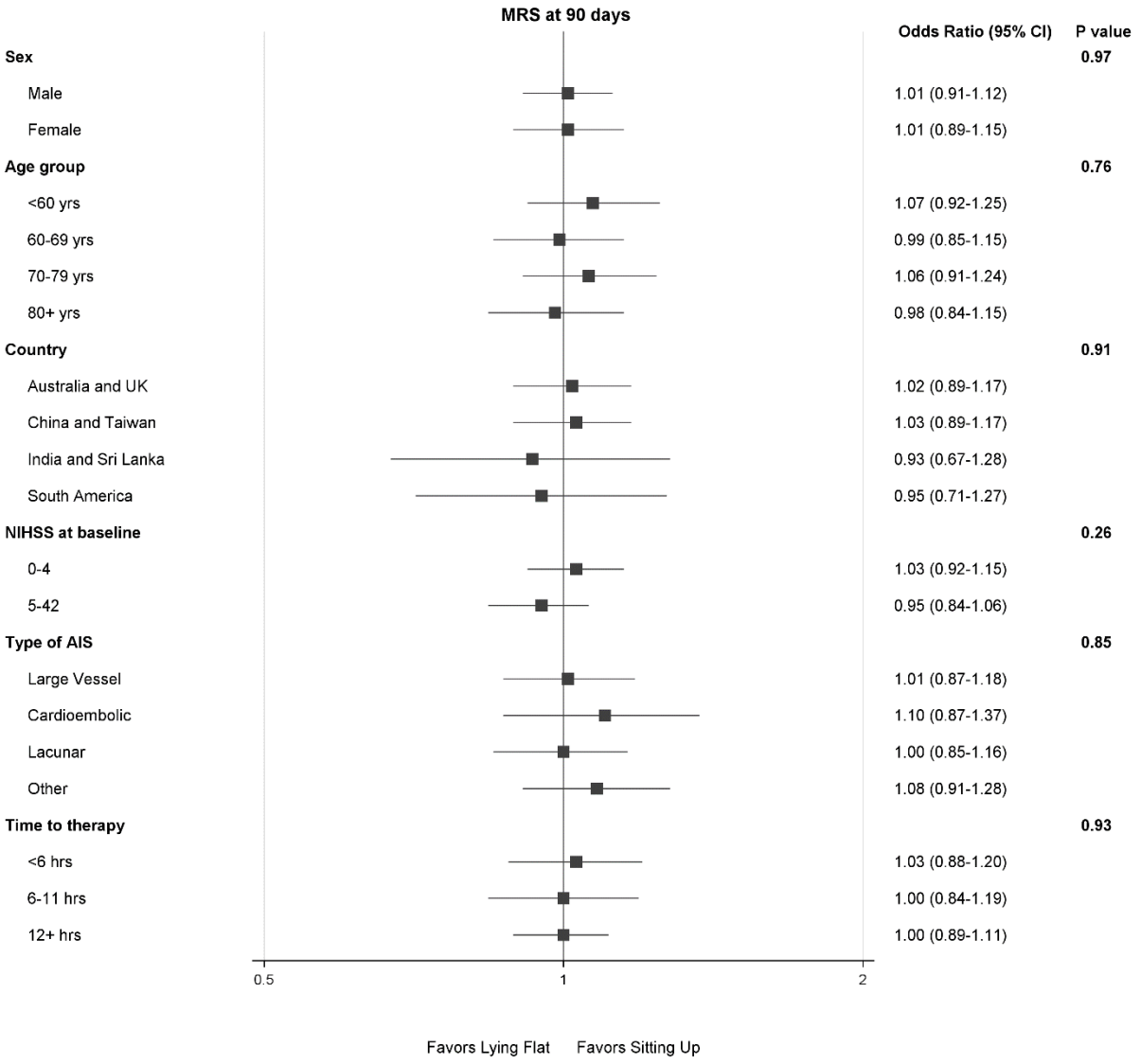
Figure S4. Kaplan-Meier curves for the probability of death at 90 days for patients in the lying-flat and sitting-up groups



Number of patients at risk :

Lying Flat :	**5216**	**4956**	**4900**	**4862**	**4826**	**4793**	**0**
Sitting Up :	**5724**	**5430**	**5358**	**5314**	**5293**	**5253**	**0**

Figure S5. Effects of lying-flat compared to sitting-up on the primary efficacy outcome (ordinal shift analysis the full range of modified Rankin scale scores 0-6), according to predefined subgroups*



*AIS denotes acute ischemic stroke, CI confidence interval, MRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent 95% CIs. For NIHSS score, values are above and below median of distribution. AIS categories were clinician-reported at the time of hospital discharge.

Figure S6. Distribution in shift across categories of National Institute of Health Stroke Scale (NIHSS) and death at 7 days

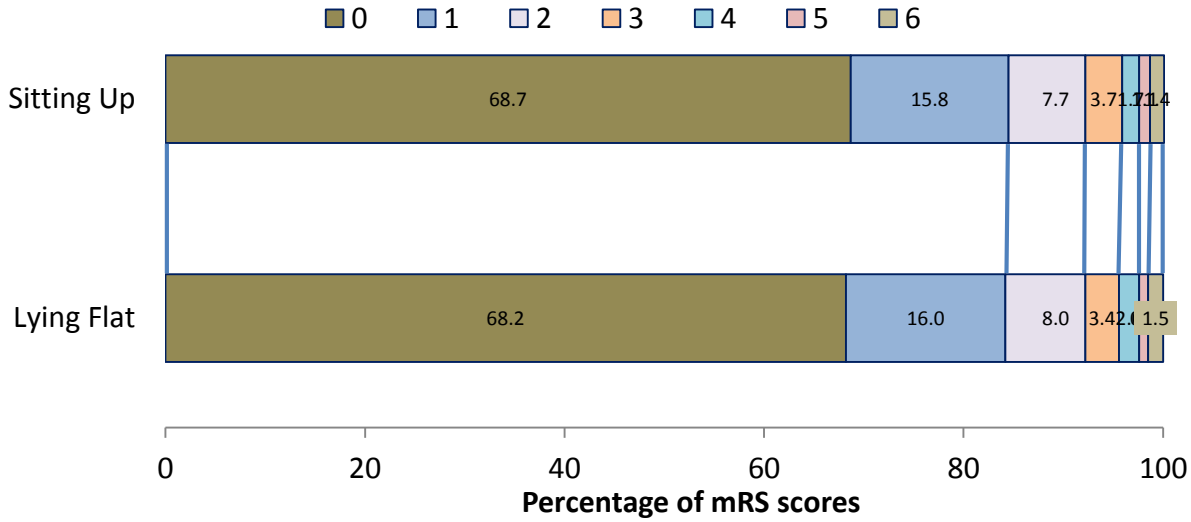


Figure S7. Distribution in shift across categories of modified Rankin scale at 7 days

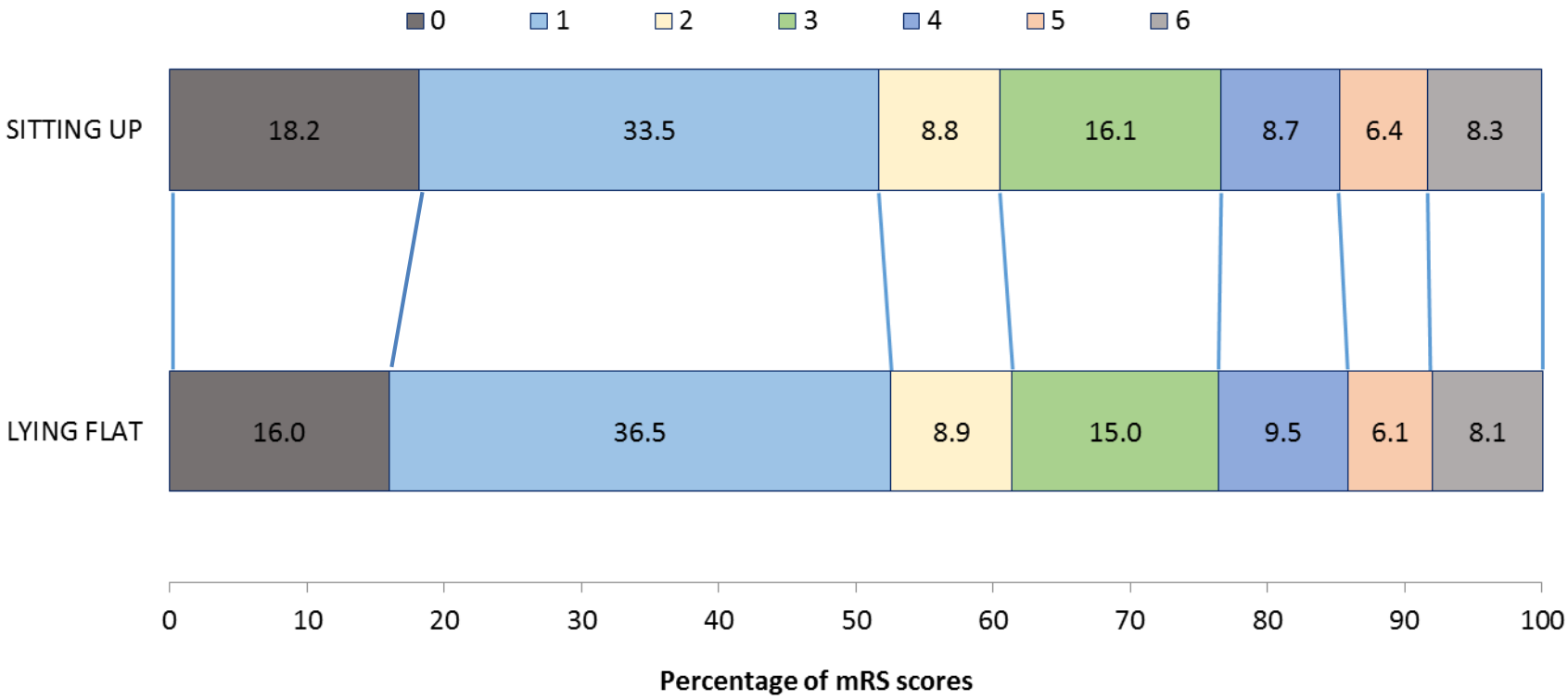
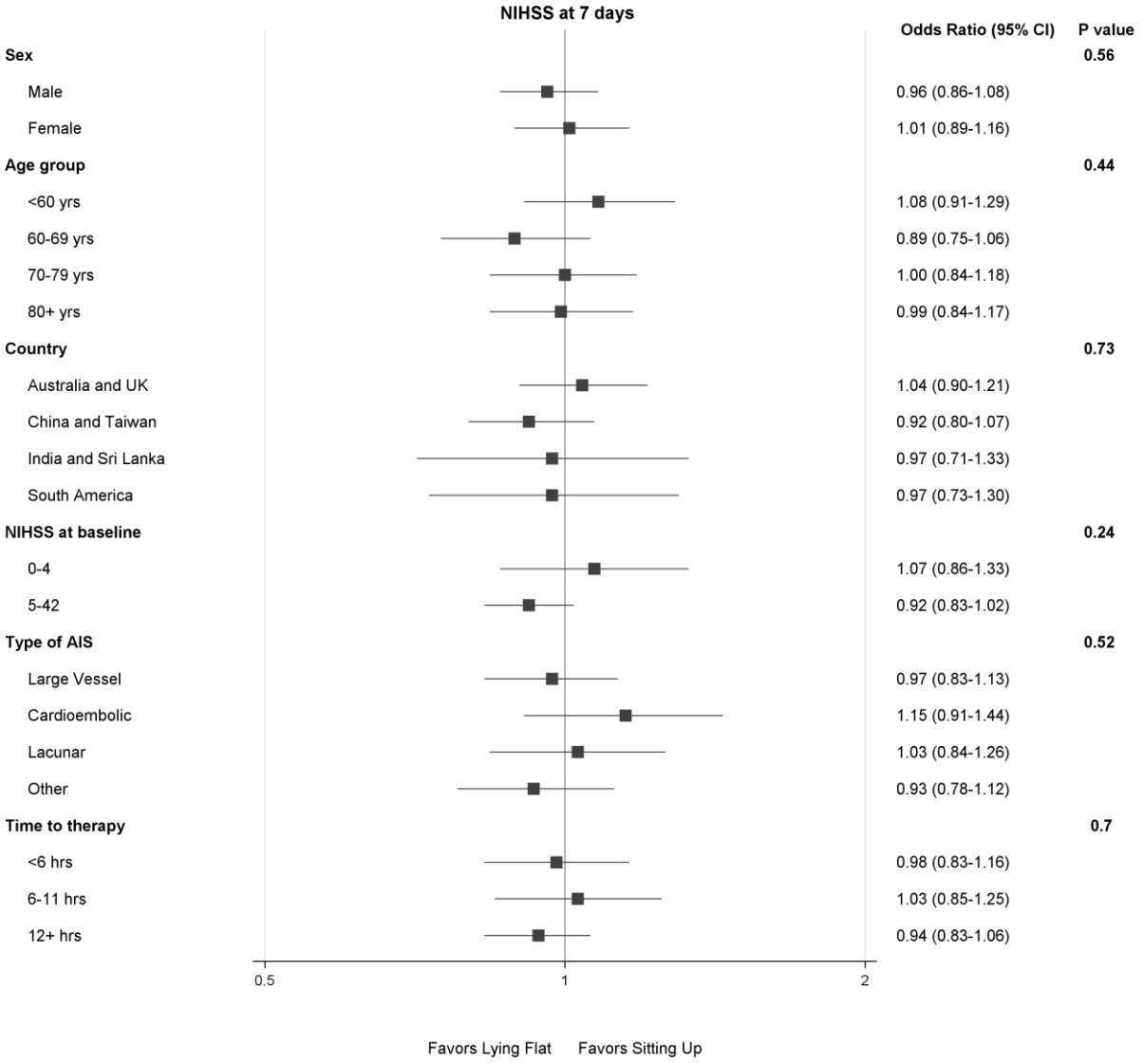
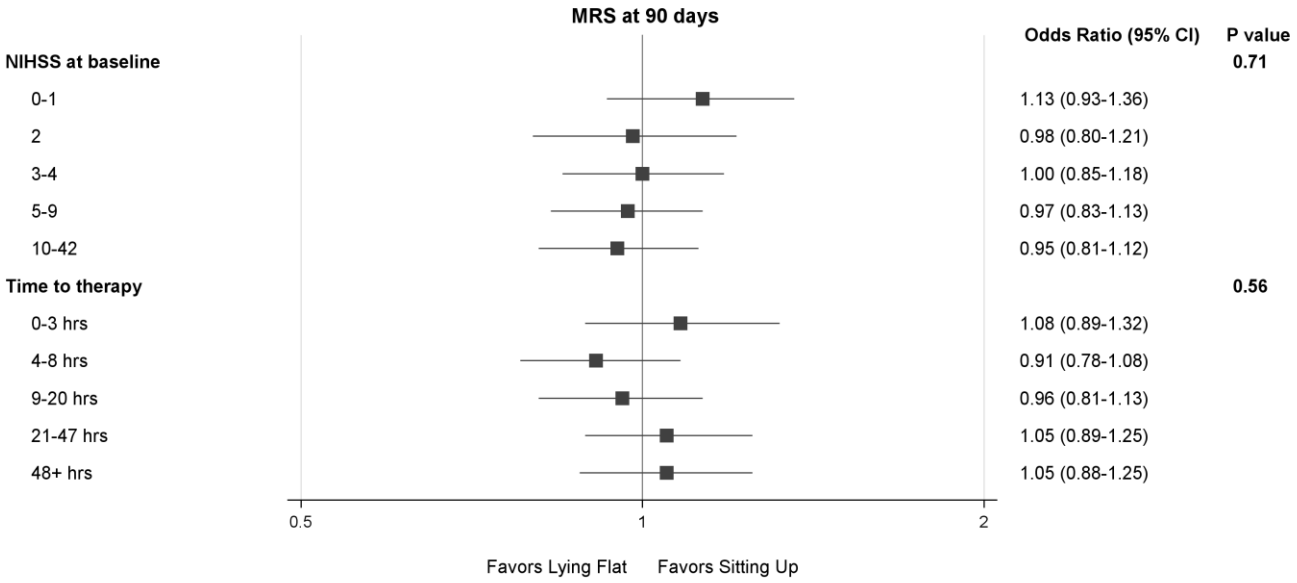


Figure S8. Treatment effect in prespecified subgroups by distribution in shift across categories of National Institute of Health Stroke Scale (NIHSS) and death at 7 days*



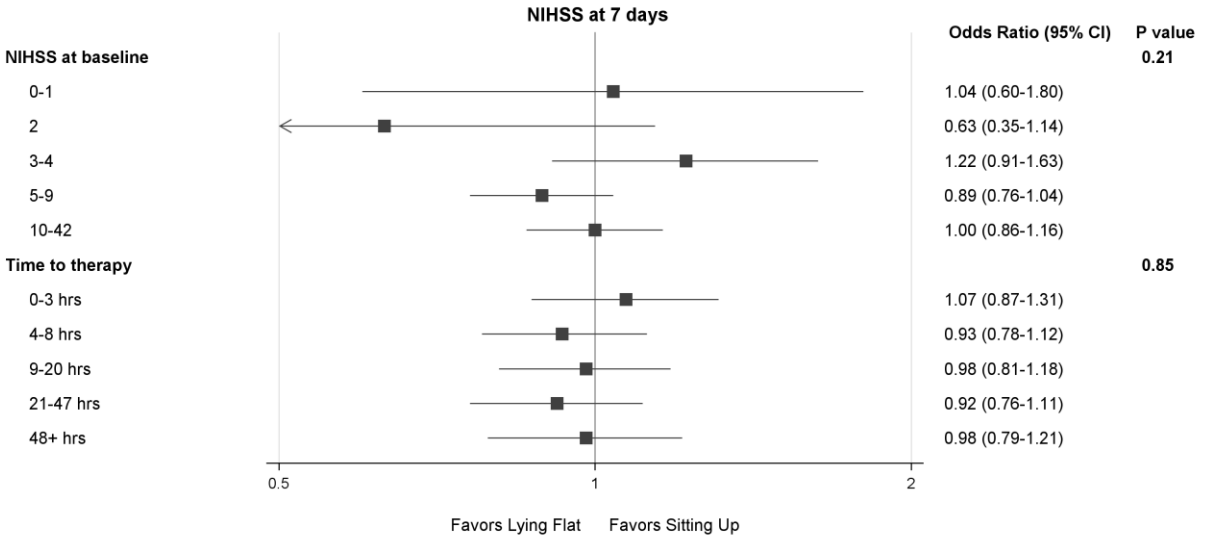
*AIS denotes acute ischemic stroke, CI confidence interval

Fig. S9. Posthoc analysis of treatment effect in prespecified subgroups by distribution in shift across quintile categories of modified Rankin scale at 90 days*



*NIHSS denotes National Institutes of Health Stroke Scale, CI confidence interval

Fig S10. Post hoc analysis of treatment effect in prespecified subgroups of baseline National Institutes of Health Stroke Scale (NIHSS) score and time from stroke onset to commencement of head position ('time to therapy'), by distribution in shift across quintile categories of NIHSS and death at 7 days



*CI denotes confidence interval

16. References

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