

**Statistical analysis plan for the family-led rehabilitation
after stroke in India (ATTEND) trial: a multicentre
randomised controlled trial of a new model of stroke
rehabilitation compared to usual care**

Journal:	<i>International Journal of Stroke</i>
Manuscript ID	Draft
Manuscript Type:	Protocol
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Billot, Laurent; The George Institute for Global Health, Statistics; The University of Sydney, Sydney Medical School Lindley, Richard; The University of Sydney, Sydney Medical School; George Institute for Global Health, Harvey, Lisa; University of Sydney, Rehabilitation Studies Unit, Northern Clinical School, Sydney School of Medicine Maulik, Pallab; George Institute for Global Health India, Research and Development; University of Oxford, The George Institute for Global Health Hackett, Maree; The George Institute for Global Health, Neurological & Mental Health Division, The University of Sydney; The University of Central Lancashire, School of Health Murthy, G.V.S; Indian Institute of Public Health Hyderabad, Anderson, Craig S.; Royal Prince Alfred Hospital and University of Sydney, The George Institute for International Health Shamanna, Bindiganavale; University of Hyderabad, School of Medical Sciences Jan, Stephen; The George Institute for Global Health, University of Sydney, Walker, Marion; University of Nottingham, Rehabilitation and Ageing Forster, Anne; University of Leeds and Bradford teaching Hospital NHS Foundation Trust, Academic Unit of Elderly Care and Rehabilitation Langhorne, Peter; University of Glasgow Verma, Shweta; Stroke Unit, Neurology Felix, Cynthia; The George Institute for Global Health, Alim, Mohammed; The George Institute for Global Health, India, Gandhi, Dorcas; Christian Medical College, Ludhiana, Punjab, India, Department of Physiotherapy Pandian, Jeyaraj; Christian Medical College, Stroke Unit, Department of Neurology</p>
Keywords:	Rehabilitation, statistical analysis plan, Cost factors, India, Clinical trial, disability, caregivers, Developing countries

**Statistical analysis plan for the family-led rehabilitation after stroke in
India (ATTEND) trial: a multicentre randomised controlled trial of a new
model of stroke rehabilitation compared to usual care**

Laurent Billot^{1,2}

Richard I Lindley^{1,2}

Lisa Anne Harvey²

Pallab Kumar Maulik^{3,4}

Maree Lisa Hackett^{1,5}

Gudlavalleti Venkata Satyanarayana Murthy⁶

Craig S Anderson^{1,2}

Bindiganavale Ramaswamy Shamanna⁷

Stephen Jan¹

Marion Walker⁸

Anne Forster⁹

Peter Langhorne¹⁰

Shweta Jain Verma¹¹

Cynthia Felix³

Mohammed Alim³

Dorcas Beulah Chandramathy Gandhi¹¹

Jeyaraj Durai Pandian¹¹

1. The George Institute for Global Health, University of Sydney, Sydney,
Australia

2 Sydney Medical School, University of Sydney, Sydney Australia

3. Research and Development, George Institute for Global Health India, Unit 301, Second Floor ANR Centre, Road No 1, Banjara Hills, Hyderabad, Telangana, India
4. The George Institute for Global Health, Oxford University, Oxford, UK
5. University of Central Lancashire, Preston, Lancashire, UK
6. Indian Institute of Public Health, Hyderabad, India & Clinical Research Department, London School of Hygiene & Tropical Medicine, London, UK
7. School of Medical Sciences, University of Hyderabad, Gachibowli, Hyderabad, India
8. School of Medicine, University of Nottingham, Nottingham, UK
9. University of Leeds, Leeds, UK
10. University of Glasgow, Glasgow, UK
11. Christian Medical College, Ludhiana, Punjab, India

Corresponding author

Professor Richard I Lindley

richard.lindley@sydney.edu.au

The George Institute for Global Health
AUSTRALIA
Level 3, 50 Bridge St
Sydney NSW 2000 Australia

Postal Address: PO Box M201
Missenden Rd
NSW 2050
Australia

T +61 2 8052 4418 | F +61 2 9657 0301

Key words

Rehabilitation

Statistical analysis plan

Cost factors

India

Clinical trial

Disability

Caregivers

Developing countries

Word count

1071 (main text and references)

References 7**Tables 0****Figures 0****Appendix ATTEND Statistical Analysis Plan****Clinical Trials Registrations**

India CTRI/2013/04/003557

Australian New Zealand Clinical Trials Registry ACTRN1261000078752

Universal Trial Number U1111-1138-6707

Funding

This study is funded by the National Health and Medical Research Council of

Australia (Project grant no APP1045391).

Pallab K Maulik is a recipient of an Intermediate Career Fellowship of Wellcome Trust-Department of Biotechnology India Alliance.

Maree L Hackett is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017).

Stephen Jan is the recipient of an NHMRC Senior Research Fellowship.

Craig Anderson holds an NHMRC Senior Principal Research Fellowship.

Conflicts of interest

We report no relevant conflicts of interest

For Review Only

Abstract

Background: In low- and middle-income countries, few patients with receive organised rehabilitation after stroke, yet the burden of chronic diseases such as stroke is increasing in these countries. Affordable models of effective rehabilitation could have a major impact. The ATTEND trial is evaluating a family-led caregiver delivered rehabilitation program after stroke.

Objective: To publish the detailed statistical analysis plan for the ATTEND trial prior to trial unblinding.

Methods: Based upon the published registration and protocol, the blinded steering committee and management team, led by a trial statistician, have developed a statistical analysis plan. The plan has been informed by the chosen outcome measures, the data collection forms and knowledge of key baseline data.

Results: The resulting statistical analysis plan is consistent with best practice and will allow open and transparent reporting.

Conclusions: Publication of the trial statistical analysis plan reduces potential bias in trial reporting, and clearly outlines pre-specified analyses.

As infectious disease has been brought under increasing control, non-communicable diseases are on the rise, with stroke, in particular, increasing in incidence and subsequent burden. The majority of those with stroke live in low and middle-income countries, and these countries have few organised stroke services.[1] In India, for example, most stroke patients do not have access to formal rehabilitation.[2] In rural areas of India, few patients get to hospital and most do not receive appropriate secondary preventative treatment.[3] Economic drivers are clearly important as the per capita Gross Domestic Product is more than thirty times greater in countries such as the USA or Australia, as compared to India.[4] Affordable healthcare should therefore be a public health priority. The ATTEND trial of family led rehabilitation after stroke is an international attempt to address this priority as recommended by the World Bank and World Health Organisation report on Disability.[5] ATTEND is an individual subject randomised controlled trial involving the training of the patient and nominated carer in key aspects of stroke rehabilitation, with an emphasis on repeated performance in task-specific activities. The intervention was piloted,[6] and then refined with input from the steering committee and project research team in Indian.

ATTEND uses a pragmatic design and the protocol has been published.[7] In brief, it is a randomised controlled trial across 14 sites in India. Patients are eligible if they are adults (aged 18 years or older) who were admitted to hospital with a recent (<1 month) stroke (ischaemic, haemorrhagic or

undifferentiated) and had residual disability with a reasonable expectation of survival. Participants need to have had a nominated caregiver and be willing to adhere to the follow-up arrangements. After consent has been obtained from both the patient and caregiver, they were randomised through a secure web-based randomisation system to either intervention or control. The intervention was started in hospital, with an aim of participants receiving it for one hour each day until discharge, delivered by a trained stroke coordinator (usually with a physiotherapy background). Part of the intervention involved discharge planning. After discharge, the patient and carer were supported by up to five home visits by a stroke coordinator who provided them with an illustrated ATTEND manual outlining key activities. The details of the intervention have been kept confidential until the trial follow-up period has been completed to reduce the risk of contamination between intervention and control patients. Overall, the intervention was developed from new models of care emerging in India, incorporating aspects of the best evidence for stroke rehabilitation and good practice summarised in an intervention guide for the stroke coordinators. Control patients received usual care. Baseline, demographic and initial follow-up data were collected at hospital discharge. Outcomes were collected at 3 months and 6 months post-randomisation by blinded assessors employed at each site. The primary outcome is the mRS at 6 months to reflect the lasting effects of the intervention on disability. The 3-month data will be used to explore trajectories of recovery and to minimise dropouts (for example, if a patient cannot be found at 3-months there will be another 3 months to try and locate the patient for the primary outcome). The main outcome was a dichotomous outcome on the modified Rankin Scale

(mRS) score of 0-2 versus 3-6, with an ordinal analysis as a key secondary outcome. Other outcomes include basic activities of daily living, quality of life, carer burden, anxiety and depression, and extended activities of daily living. Length of stay, place of residence and return to work will also be collected, as part of a larger planned economic analysis.

The trial is funded by the National Health and Medical Research Council of Australia and recruitment commenced in January 2014 and was successfully completed (1250 participants) in early 2016. In keeping with best practice, the trial is registered and the protocol published.[7] Prior to unblinding, we present the statistical analysis plan (see supplement) which helps prevent undue emphasis on data dependent analyses and reduces potential bias in future reporting. The preliminary results are expected to be announced at the World Stroke Congress in Hyderabad in October 2016.

Results from ATTEND trial have the potential to have major impact as the costs are likely to be modest, and therefore affordable to those not only in India but in other low- and middle income countries. If successful in the context of stroke, further work exploring similar models (a “polypill” of rehabilitation) would be important for other acutely disabling conditions such as hip fracture, spinal cord injury, burns and brain injury given the burden of disease in low and middle-income countries.

References

1. Feigin, V.L., et al., *Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010*. *Lancet*, 2014. **383**: p. 245-255.
2. Langhorne, P., L. de Villiers, and J.D. Pandian, *Applicability of stroke-unit care to low-income and middle-income countries*. *The Lancet Neurology*, 2012. **11**(4): p. 341-348.
3. Kalkonde, Y., et al., *Awareness and Healthcare Seeking for Stroke in Rural Gadchiroli, India: A community-based study*. *Neuroepidemiology*, 2015. **45**: p. 325.
4. Dieleman, J.L., et al., *National spending on health by source for 184 countries between 2013 and 2040*. *The Lancet*, 2016. **387**(10037): p. 2521-2535.
5. *World Report on Disability*. 2011: World Health Organisation.
6. Pandian, J.D., et al., *FAMILY-LED REHABILITATION AFTER STROKE IN INDIA: THE ATTEND PILOT STUDY*. *International Journal of Stroke*, 2015. **10**(4): p. 609-14.
7. Alim, M., et al., *Family-led rehabilitation after stroke in India: the ATTEND trial, study protocol for a randomized controlled trial*. *Trials*, 2016. **17**(1): p. 1-8.