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**Statistical analysis plan for the Head Position in Stroke Trial (HeadPoST): an international cluster cross-over randomised trial**

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**Abstract**

**Background:** There is evidence to indicate that the lying flat head position increases cerebral blood flow and oxygenation in patients with acute ischemic stroke, but how these physiological effects translate into clinical outcomes is uncertain. ~~Uncertainty exists over the optimum position for the head of a patient with acute stroke.~~ The Head Position in Stroke Trial (HeadPoST) aims to determine the comparative effectiveness of lying flat (0°) compared to sitting up (≥30°) head positioning, initiated within 24 hours of hospital admission for patients with acute stroke.

**Design:** An international, pragmatic, cluster randomised, crossover, open, blinded outcome assessed clinical trial. Each hospital with an established acute stroke unit (cluster) site was required to recruit up to ~~70~~ 140 consecutive cases of acute stroke (one phase of head positioning before immediately crossing over to the other phase of head positioning), including both acute ischaemic stroke and intracerebral haemorrhage, in each randomised head position as a 'business as usual' policy.

**Objective:** To outline in detail the predetermined statistical analysis plan (SAP) for the study.

**Methods:** All accumulated data will be reviewed and formally assessed. Information regarding baseline characteristics of patients, their process of care and management will be outlined, and for each item, statistically relevant descriptive elements will be described. For the trial outcomes, the most appropriate statistical comparisons are described.

**Results**: A SAP was developed that is transparent, verifiable, and predetermined before completion of data collection.

**Conclusions:** We developed a predetermined SAP for HeadPoST to avoid analysis bias arising from prior knowledge of the findings, in order to reliably quantify the benefits and harms of lying flat versus sitting up early after the onset of acute stroke.

**Trial registration:** ClinicalTrials.gov identifier NCT02162017; ANZCTR identifier ACTRN12614000483651

Uncertainty exists over the optimum position of the head of a patient with acute stroke. Surveys indicate variation in clinical practice, with few specific protocols used and lack of consensus over the most appropriate policy.[1-3] Some stroke guidelines provide recommendations based on a sensible extrapolation of the evidence from ventilated patients and those with head trauma, as the data pertaining to stroke patients are limited.[4-8]

A strong rationale can be made of benefits to be derived from sitting up to reduce intracranial pressure (ICP) in acute intracerebral haemorrhage (ICH)[9] or severe acute ischaemic stroke (AIS). Yet, although a systematic review of observational studies indicates that lying flat is associated with a significant increase in ICP in patients with brain injury,[10] only small changes in ICP have been noted with such head positioning in patients with large hemispheric AIS.[11]

An argument has recently arisen for potential benefits on the ischaemic penumbra of lying flat through augmentation of cerebral blood flow (CBF), based on observational studies showing increased mean flow velocity (MFV) of the middle cerebral artery on transcranial doppler (TCD); an hypothesis being tested in the Head Position in Stroke Trial (HeadPoST) Pilot trial.[12,13,14] Moreover, several studies indicate that cerebral perfusion and oxygenation is reduced with elevation of the head of patients early after ischaemic stroke[15] and when healthy older subjects stand up.[16] A counter-argument against ~~such~~ the lying flat positioning, though, is that it can increase the risk of pneumonia, particularly in those fed with a nasogastric tube or mechanically ventilated.[~~15~~17,~~16~~ 18] However, a recent study suggests that such concerns are unjustified, as a very low frequency (4.5-6%) of pneumonia was found in AIS patients who lay flat following thrombolysis treatment.[~~17~~ 19] Furthermore, swallowing is an active process independent of gravity, and any cardiorespiratory risks from lying flat are likely reduced in non-ventilated patients through actions such as ‘side-lying’ and avoidance of feeding.[~~18~~20,~~19~~21]

Whilst sitting up is common in-hospital care practice in western countries, an increasing number of stroke services have introduced the lying flat position for AIS patients on the basis of

encouraging data from small observational studies showing increased CBF on TCD.[11,12] Such a policy is further supported by the most recent American Heart Association / American Stroke Association Guidelines for the Early Management of Patients With Acute Ischemic Stroke where cautious recommendations were made for use of the lying flat head position in non-hypoxic patients without airway obstruction or aspiration risk.[22] Conversely, in low-income countries, where most of the global stroke burden exists, the lying flat position (and more prolonged immobilisation) is widely applied due to use of simple non-mechanical beds. Taken together with other geographical variations in nursing practices and hospital care policies,[20,23] the manner in which acute stroke patients are nursed could be highly relevant to variable outcomes and adverse events from this critical illness across the world.

We initiated the HeadPoST study, as nursing care for stroke patients is a universal requirement and their correct positioning is an important clinical question. The aim is to determine the comparative effectiveness (and safety) of the lying flat versus sitting up head position in patients with acute stroke.[21–23] Given uncertainty over the relevance of any treatment effects on a surrogate measure, such as increased CBF after AIS,[22,25,26] the study has been powered to determine effects on hard clinical endpoints assessed by trained personnel blind to treatment allocation. The use of broad inclusion criteria will allow an assessment of any heterogeneity of potential benefits (and harms) between AIS and ICH, and across particular subtypes of AIS, for example lacunar versus large artery occlusion. The cluster randomised crossover design was adopted to provide efficiency gains in recruitment and for assessment of likely, modest treatment effects, whilst the pragmatic approach to the implementation of the intervention across a wide range of hospital stroke services in different countries, should enhance the external validity (generalisability) of the results. Finally, the use of remote and site monitoring procedures was to ensure adherence to the protocol, fidelity of the intervention, and high quality standards of data collection and participant registration and management.

The trial includes two important design features. A cluster guardian consent process was obtained from a senior executive officer at each site to apply the intervention to patients as part of routine care; and opt-in (or opt-out in all centers in Australia) written informed consent was obtained from participants, or their approved surrogate, for collection of medical data and participation in follow-up assessments. Moreover, the eligibility criteria were kept simple to facilitate implementation of the randomised head position as routine policy for nursing care, and were based on the uncertainty principle: only patients with clear indications for or contraindications to either head position, as assessed by the local physician and taking into account local guidelines and standards of practice, were excluded from participation. In addition, patients were only excluded if it was considered that the allocated head position could not be applied consistently, the neurological symptoms were reversible (i.e. diagnosis of transient ischemic attack) or not stroke related, or if they refused participation.

Herein, we describe the statistical analysis plan (SAP) for HeadPoST (see Appendix S1), which was finalised prior to completion of the data collection, and is what investigators will adhere to in analysing the results of the study. The SAP was approved and signed off by the study Steering Committee in October 2016, following completion of participant recruitment in August 2016, and before final patient follow-up in December 2016. The statistical analyses specified in the SAP occurred in January 2017.

The HeadPoST study has been designed to provide reliable evidence about the efficacy. effectiveness and safety, of a simple nursing intervention in order to provide reliable evidence to inform policy in the early management of patients with AIS and ICH.

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**Disclaimers**

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