Stroke research in WA

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- Research Coordinators
  - Anne Claxton
  - Nicole O’Loughlin

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  - Gill Edmonds
  - Sarah D’Souza

- Trainees
  - Neha Khade
  - Muhammad Aaquib
  - Alison Rothnie
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Current trials and projects
The **Assessment of Fluoxetine In Stroke recovery (AFFINITY)** trial

- Stroke is one of the top three causes of disability.
- Treatments that improve recovery after stroke are lacking.
- This trial aims to find out whether fluoxetine, given in the first two weeks after stroke to 1600 participants, and continued for 6 months, is safe and improves recovery at 6 months compared to a placebo.

**PI:** Professor Graeme Hankey, SCGH and UWA
- Associate Professor Maree Hackett, The George Institute for Global Health & The University of Sydney
Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

François Chollet, Jean Tardy, Jean-François Albucher, Claire Tholarnos, Emilié Berard, Catherine Lamy, Yannick Bejet, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoît Guillot, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Summary

Background  Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials suggest that fluoxetine enhances motor recovery but its clinical efficacy is unknown. We therefore aimed to investigate whether fluoxetine would enhance motor recovery if given soon after an ischaemic stroke to patients who have motor deficits.

Methods  In this double-blind, placebo-controlled trial, patients from nine stroke centres in France who had ischaemic stroke and hemiplegia or hemiparesis, had Fugl-Meyer motor scale (FMMS) scores of 55 or less, and were aged between 18 years and 85 years were eligible for inclusion. Patients were randomly assigned, using a computer random-number generator, in a 1:1 ratio to fluoxetine (20 mg once per day, orally) or placebo for 3 months starting 5–10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug. Participants, carers, and physicians assessing the outcome were masked to group assignment. Analysis was of all patients for whom data were available (full analysis set). This trial is registered with ClinicalTrials.gov, number NCT00657163.

Findings  118 patients were randomly assigned to fluoxetine (n=59) or placebo (n=59), and 113 were included in the analysis (57 in the fluoxetine group and 56 in the placebo group). Two patients died before day 90 and three withdrew from the study. FMMS improvement at day 90 was significantly greater in the fluoxetine group (adjusted mean 34.0 points [95% CI 29.7–38.4]) than in the placebo group (24.3 points [19.9–28.7]; p=0.003). The main adverse events in the fluoxetine and placebo groups were hypotension (two [4%] vs two [4%]), transient digestive disorders including nausea, diarrhoea, and abdominal pain (14 [25%] vs six [11%]), hepatic enzyme disorders (five [9%] vs ten [18%]), psychiatric disorders (three [5%] vs four [7%]), insomnia (19 [33%] vs 20 [36%]), and partial seizure (one [<1%] vs 0).

Interpretation  In patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy enhanced motor recovery after 3 months. Modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of patients with ischaemic stroke and moderate to severe motor deficit.
Eligibility criteria

**Inclusion Criteria**

Men or women aged ≥ 18 years with all of the following:

- Clinical diagnosis of stroke 2-15 days previously (Day of stroke onset = Day 0, randomise on Day 2-15)
- Brain imaging consistent with ischaemic or haemorrhagic (intracerebral and/or subarachnoid) stroke (including normal CT brain scan)
- Persisting measurable focal neurological deficits (e.g. motor, somatosensory, visual, language, cognitive) present at randomisation and severe enough to produce a modified Rankin Scale (mRS) score of ≥1 and to warrant treatment from the perspective of patient or carer(s)

**Exclusion Criteria**

Any of the following:

- History of epileptic seizures
- History of bipolar disorder
- History of drug overdose or attempted suicide
- Ongoing treatment with any selective serotonin reuptake inhibitor (SSRI)
- Allergy or contra indication to fluoxetine including
  - Hepatic impairment (serum alanine aminotransferase [ALT] > 120 U/l),
  - Renal impairment (creatinine > 180 micromol/l or eGFR < 30 ml/min/1.73m²),
  - Hyponatremia (sodium < 125mmol/L) despite treatment of the cause and confirmed on repeat testing,
- Use of medications that may interact seriously with fluoxetine
  - Proposed use of a monoamine oxidase inhibitor (MAOI), or use of a MAOI within 14 days prior to randomisation
  - Current treatment with an antipsychotic drug (neuroleptic), pimozide, tamoxifen, or tramadol, unless the patient, doctor and if possible prescribing doctor believe it is appropriate to discontinue use.
- Not available for follow up over the next 365 days e.g. no fixed home address
- Life-threatening illness (e.g. advanced cancer) that is likely to reduce 365 day survival
- Pregnant, breast-feeding or of child-bearing potential and not using contraception
AFFINITY – recent updates

**AFFINITY Recruitment**

Updated: 13th October 2017

- **Total No. Sites:** 32
- **Total No. Participants Recruited:** 398

- **Recruitment Progress**
  - Recruitment target: 1600 participants
  - Total affinity patients randomised to date: 401
  - Total participants on the MRI Sub Study: 8
  - Total participants on the DNA Sub Study: 29
The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials

Gillian Mead1, Maree L. Hackett2, Erik Lundström3, Veronica Murray1*, Graeme J. Hankey2 and Martin Dennis1*

Abstract

Background: Several small trials have suggested that fluoxetine improves neurological recovery from stroke. FOCUS, AFFINITY and EFFECTS are a family of investigator-led, multicentre, parallel group, randomised, placebo-controlled trials that aim to determine whether routine administration of fluoxetine (20 mg daily) for 6 months after acute stroke improves patients' functional outcome.

Methods/Design: The three trial investigator teams have collaboratively developed a core protocol. Minor variations have been tailored to the national setting in the UK (FOCUS), Australia and New Zealand (AFFINITY) and Sweden (EFFECTS). Each trial is run and funded independently and will report its own results. A prospectively planned individual patient data meta-analysis of all three trials will subsequently provide the most precise estimate of the overall effect of fluoxetine after stroke and establish whether any effects differ between trials and subgroups of patients.

The trials include patients ≥18 years old with a clinical diagnosis of stroke, persisting focal neurological deficits at randomisation between 2 and 15 days after stroke onset. Patients are randomised centrally via web-based randomisation systems using a common minimisation algorithm. Patients are allocated fluoxetine 20 mg once daily or matching placebo capsules for 6 months. Our primary outcome measure is the modified Rankin scale (mRS) at 6 months. Secondary outcomes include the Stroke Impact Scale, EuroQol (EQ5D-5 L), the vitality subscale of the Short-Form 36, diagnosis of depression, adherence to medication, adverse events and resource use. Outcomes are collected at 6 and 12 months. The methods of collecting these data are tailored to the national setting. If FOCUS, AFFINITY and EFFECTS combined enrol 6000 participants as planned, they would have 90% power (alpha 5%)

to detect a common odds ratio of 1.16, equivalent to a 3.7% absolute difference in percentage with mRS 0–2 (44.0% to 47.7%). This is based on an ordinal analysis of mRS adjusted for baseline variables included in the minimisation algorithm.

Discussion: If fluoxetine is safe and effective in promoting functional recovery, it could be rapidly, widely and affordably implemented in routine clinical practice and reduce the burden of disability due to stroke.


Keywords: Ischaemic stroke, Haemorrhagic stroke, Antidepressants, SSRI, Fluoxetine, Recovery, Depression
Embolic Stroke of Undetermined Source
A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana Catanese, MD; Kanjana S. Perera, MBBS; George Ntaios, MD, PhD; Stuart J. Connolly, MD

Table 1. Criteria for Diagnosis of Embolic Stroke of Undetermined Source (ESUS)∗

| 1. Ischemic stroke detected by CT or MRI that is not lacunar† |
| 2. Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia |
| 3. No major risk cardioembolic source of embolism‡ |
| 4. No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, and drug abuse) |
Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: Design of the NAVIGATE ESUS randomized trial

Figure 1. NAVIGATE ESUS design overview.

Table 2. Key exclusion criteria.

1. Severely disabling stroke (modified Rankin score ≥4 at screening)
2. Patent foramen ovale with plans for closure
3. Known serious infection or inflammatory disease that may be the cause of stroke
4. Patient has or is intended to receive an implantable ECG loop recorder
5. Indication for chronic anticoagulation
6. Indication for chronic antiplatelet therapy
7. Active bleeding/major bleeding within last six months/previous nontraumatic intracranial hemorrhage (any type, ever)/high risk for serious bleeding
8. Hepatic disease associated with coagulopathy
9. Renal disease with estimated GFR < 30 ml/min/1.73 m²
10. Life expectancy less than six months
11. Use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (e.g. protease inhibitors and several azole-antifungal agents)
12. Female of childbearing potential who is not surgically sterile or who is sexually active and not using reliable contraception
13. Chronic, regular use of a conventional nonsteroidal anti-inflammatory drug

Figure 2. Countries participating in NAVIGATE ESUS.
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Recruitment Summary by Country
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</table>

**Recruitment Summary by Country**

- **Recruitment in Previous Months**
  - JUN 2017
  - JUL 2017
  - AUG 2017
  - SEP 2017
  - Randomization Rate
  - Month in Previous 8 Weeks

- **Sites Inactive for > 30 Days**
  - 31 - 60 Days
  - 51 - 120 Days
  - > 120 Days

- **Sites Total**
  - Recruitment
  - 31 - 60 Days
  - 51 - 120 Days
  - > 120 Days
<table>
<thead>
<tr>
<th>Site ID</th>
<th>Institution Name</th>
<th>PI Name</th>
<th>Date Activated for Random</th>
<th>Months able to randomize</th>
<th>Days able to randomize</th>
<th>Randomization Rate Site Month</th>
<th>Randomization Rate Site Month in Last 8 Weeks</th>
<th>Total Randomizations</th>
<th>Date of last pt randomized</th>
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<td>50</td>
<td>Monash Health</td>
<td>Thanh Phan</td>
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<tr>
<td>60</td>
<td>Calvary Mater Hospital</td>
<td>Elizabeth Pepper</td>
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<td>Launceston General Hospital</td>
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<td></td>
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<td></td>
<td>119</td>
<td>2017-09-20</td>
</tr>
</tbody>
</table>
NAVIGATE ESUS Study Stopped Early Due to Comparable Efficacy in Treatment Arms

*Phase III study evaluated rivaroxaban versus aspirin in patients with embolic stroke of undetermined source with no atrial fibrillation*

Study unlikely to show benefit of rivaroxaban versus aspirin if it were to be completed

RARITAN, NJ (October 5, 2017) — Janssen Research & Development, LLC and its development partner Bayer today announced the Phase III NAVIGATE ESUS study, evaluating the efficacy and safety of Xarelto® (rivaroxaban) for the secondary prevention of stroke and systemic embolism in patients with a recent embolic stroke of undetermined source (ESUS), is stopping early for futility. This decision is based on the recommendation of the study’s Independent Data Monitoring Committee (IDMC) as the trial showed comparable efficacy between rivaroxaban and the standard of care, aspirin, and little chance of rivaroxaban showing an overall benefit versus aspirin if the study were to be completed. While bleeding rates were very low overall and within the expected range, an increase in bleeding was observed in the rivaroxaban arm compared to aspirin.
Young ESUS Patient Registry (Y-ESUS)

This study is currently recruiting participants.

See Contacts and Locations

Verified June 2017 by Population Health Research Institute

Sponsor:
Population Health Research Institute

<table>
<thead>
<tr>
<th>First Submitted Date</th>
<th>June 9, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Posted Date</td>
<td>June 14, 2017</td>
</tr>
<tr>
<td>Last Update Posted Date</td>
<td>June 14, 2017</td>
</tr>
<tr>
<td>Actual Start Date</td>
<td>February 15, 2017</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>December 2018  (Final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Current Primary Outcome Measures  (submitted: June 9, 2017)</td>
<td>Recurrent ischemic stroke and/or death in a well-defined Young ESUS cohort [ Time Frame: Approximately 18 Months ]</td>
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</tbody>
</table>
AF detection studies – NUUBO
AF detection studies – SPOT-AF

Evaluating the efficacy of smartphone electrographic monitoring for atrial Fibrillation detection in Acute Ischemic Stroke and transient ischemic attack patients

PI: A/Prof Bernard Yan and Dr Hans Tu, Royal Melbourne hospital
For this analysis, investigators classified patients according to three groups (n = 87):

- large-artery stroke with greater than 50% stenosis but no AF (n = 30);
- small-vessel disease only and no AF (n = 27);
- cardioembolic stroke (n = 30), defined as proven AF on electrocardiography or Holter monitoring but no stenosis in a perfusing artery.

A LAVI greater than 34 mL/m2 was associated with a greater than 7-fold increased risk for cardioembolic stroke (hazard ratio, 7.1; P < .001).
Clinical Guidelines for Stroke Management 2017

- For patients with ischaemic stroke due to atrial fibrillation and a genuine contraindication to long-term anticoagulation, percutaneous left atrial appendage occlusion may be a reasonable treatment to reduce recurrent stroke risk.

PROTECT-AF study

PREVAIL – AF study
The Amulet IDE trial is a prospective, randomized, multi-center active control worldwide trial, designed to evaluate the safety and effectiveness of the AMPLATZER™ Amulet™ Left Atrial Appendage Occluder.

Subjects will be randomized in a 1:1 ratio between the Amulet LAA occlusion device (treatment) or a Boston Scientific WATCHMAN® LAA closure device (Control).

The trial will be conducted at up to 150 sites worldwide. All enrolled subjects will follow the protocol-required tests and assessments at each scheduled follow-up visit.
Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Non-valvular Atrial Fibrillation: a Real World Study in Western Australia – Dr Vincent Paul and Dr Richard Clugston

- Retrospective study of patients who underwent LAAO in Western Australia (WA) from 2010 to 2016
- 131 patients (75±8 years, 73% male) from 3 tertiary hospitals in WA were included.
- Average CHA$_2$DS$_2$-VASc score was high 4.3+/1.5
- Longterm anticoagulation contraindications included gastrointestinal (40%) and intracranial bleeding (25%)
- Incidence of neurologic events were low (n=8) (ischaemic stroke (n=5), haemorrhagic stroke (n=2) and transient ischaemic attack (n=1) and 22 patients had died at time of follow-up (34±24 months).
Prehospital stroke scales

- MASS
- CPSSS
- LEGS
- RACE >=5
  Accuracy 79%
- NIHSS >=11
  Accuracy 79%
- LAMS
- 31SS
- VAN
- WIRE
# Rapid Arterial Occlusion Evaluation (RACE)

*Note that out of a possible 11 points, due to hemiparesis a maximum score of ≤ 9 can be attained.*

<table>
<thead>
<tr>
<th>Item</th>
<th>Instruction</th>
<th>RACE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial Palsy</strong></td>
<td>Ask the patient to smile</td>
<td>Absent (symmetrical movement) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild (slightly asymmetrical) 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate to severe (completely asymmetrical) 2</td>
</tr>
<tr>
<td><strong>Arm Motor Function</strong></td>
<td><strong>Extending the arm of the patient, 90° degrees (if sitting) or 45° degrees (if supine)</strong></td>
<td>Normal to mild (limb upheld more than 10 seconds) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (limb upheld less than 10 seconds) 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (patient do not rise the arm against gravity) 2</td>
</tr>
<tr>
<td><strong>Leg Motor Function</strong></td>
<td><strong>Extending the leg of the patient 30° degrees (in supine)</strong></td>
<td>Normal to mild (limb upheld more than 5 seconds) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (limb upheld less than 5 seconds) 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (patient do not rise the leg against gravity) 2</td>
</tr>
<tr>
<td><strong>Head &amp; Gaze Deviation</strong></td>
<td>Observe eyes and head deviation to one side</td>
<td>Absent (eye movement to both sides were possible and cephalic deviation was observed) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present (eyes an cephalic deviation to one side was observed) 1</td>
</tr>
<tr>
<td><strong>Aphasia</strong></td>
<td>(for RIGHT sided hemiparesis only) Test: Understanding of words</td>
<td>Normal (performs both tasks correctly) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (performs one task correctly) 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (performs neither tasks) 2</td>
</tr>
<tr>
<td><strong>Agnosia</strong></td>
<td>(for LEFT sided hemiparesis only) Test: Cognitive recognition</td>
<td>Normal (Recognises arm, and attempts movement) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate (No arm recognition OR is unaware of arm) 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe (Unable to recognise &amp; unaware of arm) Both questions answered unconvincingly 2</td>
</tr>
</tbody>
</table>

**Score Total:** 0-9/11
**Results**

<table>
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<tr>
<th></th>
<th>LVO +ve</th>
<th>LVO -ve</th>
</tr>
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<tbody>
<tr>
<td><strong>RACE ≥ 5</strong></td>
<td>58</td>
<td>34</td>
</tr>
<tr>
<td><strong>RACE &lt; 5</strong></td>
<td>22</td>
<td>134</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>146</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td>226</td>
<td></td>
</tr>
</tbody>
</table>

**Code Stroke**

- **226 Patients**

**RACE ≥ 5**

- **LVO +**
  - Appropriate
  - 63% (95% CI: 52-73%)

- **LVO -**
  - False positives
  - 37% (95% CI: 18-39%)

**RACE < 5**

- **LVO +**
  - Missed
  - 16% (95% CI: 17-31%)

- **LVO -**
  - Appropriate
  - 84% (95% CI: 74-89%)

**False positives**

- Includes haemorrhage

**Missed**

- Improve door-in-door-out times
ORIGINAL RESEARCH

Mechanical thrombectomy for anterior circulation stroke: 5-year experience in a statewide service with differences in pretreatment time metrics across two hospitals sites

Ruchi Kabra, 1 Timothy J Phillips, 1 Jacqui-Lyn Saw, 2 Constantine C Phatouros, 1 Tejinder P Singh, 1 Graeme J Hankey, 3 David Blacker, 3 Darshan Ghia, 2 David Prentice, 2 William McAuliffe 1
Matrix for Perth Metropolitan

- **RACE ≥5 during business hours**
  - FSH from south of river
  - SCGH from north of the river

- **RACE ≥ 5 out of hours including weekends**
  - SCGH

- **RACE < 5 – any time**
  - Priority transfer to nearest tPA centre (FSH, SCGH, RPH, MPH)
  - CTA/CTP
  - Short door –in-door-out times

- **Onset > 6 hrs**
  - Transfer as per current SJA protocol

- **Onset ≤ 6 hrs**
  - RACE score
Accuracy of stroke identification by paramedics in a metropolitan pre-hospital setting: A cohort study

Teresa A Williams  
Curtin University, Australia

David Blacker  
Sir Charles Gairdner Hospital, Western Australia

Glenn Arendts  
Fiona Stanley Hospital, Western Australia

Emily Patrick  
St John Ambulance, Western Australia

Deon Brink  
St John Ambulance, Western Australia

Judith Finn  
Curtin University, Australia
Statin Study - FSH
Prof Merrilee Needham

• Prospective observational study
  • Following patients started on a statin or undergoing dose increase
  • Following CVA/TIA or ACS
  • for 6 months

• Understand
  • Incidence muscle side effects (and other including cognitive)
  • Tolerability
  • Compliance

• Investigate
  • predictive factors for the above
  • Utility of baseline CK
Enhancing recovery of function after stroke – combined use of physical training (robot-assisted arm therapy) with non-invasive brain stimulation

Principal Investigator: Clinical Professor Soumya Ghosh, Medical Director, Centre for Restorative Neurology
Co-investigators: Susan Walters, Jennifer Eisenhauer, Assoc. Prof. Ian Cooper, Jesse Dixon
Should you have questions about the study or wish to participate in the study you may contact: Jesse Dixon or Jenny Eisenhauer at the Perron clinic on 6457 0207 or jesse.dixon@health.wa.gov.au

This study aims to evaluate whether brain stimulation (transcranial direct current stimulation – tDCS) added to a computer controlled exercise (robot-guided arm therapy) will provide added benefit in recovery of the upper limb following stroke.

- First ever ischemic stroke causing arm weakness.
- Within the first 12 months following stroke, when they are discharged from inpatient care
- 2-3 weekly sessions of robotic arm therapy for 6-9 weeks (18 sessions, each about 2 hours).
- Half of the group will receive the brain stimulation and half will receive the sham stimulation.
- Regular outpatient therapy program prescribed by their rehabilitation physicians.
Pilot study of Virtual Reality Rehabilitation for stroke survivors with upper limb weakness

**Coordinating Principal Investigator:** Prof. David Blacker

**Principal Investigators:** Dr Michelle Byrnes, Dr Mohd Fairuz Shiratuddin, Dr Michael Newton, Dr Ferdous Sohel & Kevin Wong
Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial

**Interpretation** First mobilisation took place within 24 h for most patients in this trial. The higher dose, very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide, and our findings should affect clinical practice by refining present guidelines; however, clinical recommendations should be informed by future analyses of dose–response associations.
Very Early Rehabilitation in SpEech (VERSE) randomised clinical trial: Ongoing trial status.

Primary hypothesis:
• Participants receiving UC and early daily aphasia therapy have 20% greater scores than UC alone on the Aphasia Quotient (AQ) at twelve weeks post stroke.

Secondary hypotheses:
• Participants receiving *prescribed* early daily aphasia therapy have 4.5% greater scores than intensive ward based (UC+) on the Aphasia Quotient (AQ) at twelve weeks post stroke.
### Intervention

<table>
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<tr>
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<th>Usual Care</th>
<th>Usual Care-Plus</th>
<th>VERSE</th>
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<tr>
<td><strong>Usual Care</strong></td>
<td>• Usual ward based aphasia therapy</td>
<td>• Usual care plus daily ward based</td>
<td>• Usual care plus Individually</td>
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<tr>
<td></td>
<td></td>
<td>aphasia therapy</td>
<td>prescribed aphasia therapy</td>
</tr>
<tr>
<td><strong>Usual Care-Plus</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>VERSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapy Intensity:</strong></td>
<td>Therapy Intensity: Varies - expected &lt; 6 hours over 4-5 weeks</td>
<td>Therapy Intensity: 20 sessions of direct aphasia therapy of 45 – 60 mins (15-20 hours) over 4-5 weeks</td>
<td>Therapy Intensity: 20 sessions of direct aphasia therapy of 45 – 60 mins (15-20 hours) over 4-5 weeks</td>
</tr>
</tbody>
</table>
Eligibility criteria

Inclusion criteria

• Acute stroke defined by ICD-10 codes 161-164
• Aphasia of any type and score < 93.7 of the Aphasia Quotient
• Medically stable at recruitment
• Ability to maintain a wakeful alert state for 30 consecutive minutes
• Recruited within 14 days of stroke onset
• Normal or corrected hearing and vision

Exclusion criteria

• TIA, SDH or SAH
• Previous aphasia
• Head injury and or neurosurgery
• A prior diagnosis of dementia, clinically diagnosed major depression
• A concurrent progressive neurological disorder
• Unable to participate in English based therapy due to English being a second language.
<table>
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<tr>
<th>Site</th>
<th>Patient Recruitment</th>
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<td>St George (NSW)</td>
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<td>Fremantle (WA)</td>
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<tr>
<td>Cairns (Qld)</td>
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<td>St Vincent’s (VIC)</td>
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<tr>
<td>RMH (Vic)</td>
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<tr>
<td>Fiona Stanley Hospital (WA)</td>
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<td>Gold Coast (Qld)</td>
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<td>Joondalup (WA)</td>
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<td>Alfred (Vic)</td>
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<td>Concord (NSW)</td>
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<td>Tauranga (NZ)</td>
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<td>Albury-Wodonga Hospital (NSW)</td>
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<td>Prince of Wales (NSW)</td>
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<td>RPA (NSW)</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>225</strong></td>
</tr>
</tbody>
</table>
Trial completion

- Last patient, first visit (December 2017)
  - Primary Outcome: May 2018
  - Last patient, last visit: June 2018
- Final results: October 2018
Investigating a Communication Enhanced Environment (CEE) to increase communication activity early after stroke

Research team: Sarah D’Souza, Dr Heidi Janssen, Associate Prof. Natalie Ciccone, Associate Prof. Deborah Hersh, Claire Tucak, Millie Galan-Dwyer, Prof. Beth Armstrong, Associate Prof. Erin Godecke

• Pilot study to develop and test a Communication Enhanced Environment on the acute and rehabilitation wards
• Aim to increase communication and language activity for stroke survivors with aphasia
• Based on Environment Enrichment which involves exposure to a stimulating environment to create more opportunities for activity
• May potentially utilise the critical period of increased neuroplasticity early after stroke

This study has been funded by the Hollywood Private Hospital Research Foundation: RF087
Three phases

1. Baseline phase:
   • Quantify current patient communication and language activity levels
   • Determine current staff and patient perceptions of barriers and facilitators to communication
     COMPLETED, recruited 55 staff, 7 stroke patients

2. Implementation phase:
   • Develop and embed a CEE on the acute and rehabilitation wards IN PROCESS

3. Intervention phase:
   • Quantify changes in communication and language activities for stroke inpatients
   • Determine changes to staff and patient perceptions of barriers and facilitators to communication on the wards in a Communication Enhanced Environment
   • Determine staff and patients' opinions regarding their experience of a CEE

Sarah D’Souza
PhD Student, Speech Pathology, Edith Cowan University
Contact: s.dsouza@ecu.edu.au
Dysphagia and Factors Associated with Respiratory Infections in the First Week Post Stroke

Emily Brogan\textsuperscript{a,}\textsuperscript,*  Claire Langdon\textsuperscript{b}  Kim Brookes\textsuperscript{a}  Charley Budgeon\textsuperscript{c,d}  David Blacker\textsuperscript{a,e}

\textsuperscript{a}Sir Charles Gairdner Hospital, Western Australia, \textsuperscript{b}Western Australian Department of Health, \textsuperscript{c}Centre for Applied Statistics, University of Western Australia, \textsuperscript{d}Department of Research, Sir Charles Gairdner Hospital, and \textsuperscript{e}The School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia
Enhancing rehabilitation services for Aboriginal Australians after brain injury
NHMRC Partnership Project: 2017-2021

AIMS:
• To improve delivery of culturally appropriate rehabilitation services to Aboriginal people post-acquired brain injury (stroke and traumatic brain injury)
• To improve overall health outcomes for the above population
• To establish an economic model to support the business case for funding new rehabilitation services which will contribute to the planning and sustainability of future services.

DESIGN:
A stepped wedge cluster randomised control trial

RESEARCH TEAM:
CHIEF & ASSOCIATE INVESTIGATORS:
CIA Prof. Elizabeth Armstrong ECU + collaborators from ECU, UWA, Notre Dame University, Monash University & UTS

PARTNER INVESTIGATORS
Western Australian Department of Health
– Western Australia Country Health Service (Pilbara, Kimberley, Goldfields, Midwest)
– 4 Metropolitan Hospitals (Royal Perth, Sir Charles Gairdner, Fiona Stanley-Fremantle and St John of God Midland Hospitals)
Royal Perth Hospital Medical Research Foundation
Geraldton Regional Aboriginal Medical Service
Kimberley Aboriginal Medical Services
Bega Garnbirringu Health Services, Kalgoorlie
Warrika Maya Health Service, Port Hedland
Stroke Foundation and Neurological Council of WA
Other projects

01
Validation of admission vs final diagnosis of TIA/Stroke at FSH and stroke unit admissions missed.
- Alison Rothnie, FSH

02
Integrated, Computational, Preclinical and Clinical approach using non-invasive brain stimulation (rTMS) for stroke recovery
- Hakuei Fujiyama, Murdoch University

03
Music therapy in Stroke rehab
- The intervention is an iOS app that allows the person to move in time to music, wearing sensors that provide feedback about movement accuracy. The idea is they can use the app independently 3 times per week in addition to usual rehab.
- Ann-Maree Vallence, Murdoch University
ORACLE Stroke Study: Opinion Regarding Acceptable Outcome Following Decompressive Hemicraniectomy for Ischemic Stroke

BACKGROUND: There continues to be considerable interest in the use of decompressive hemicraniectomy in the management of malignant cerebral artery infarction; however, concerns remain about long-term outcome.

OBJECTIVE: To assess opinion on consent and acceptable outcome among a wide range of healthcare workers.

METHODS: Seven hundred seventy-three healthcare workers at the 2 major public hospitals in Western Australia were contacted. Participants were asked to discuss their opinion regarding acceptability of decompressive hemicraniectomy for malignant cerebral artery infarction.

Decompressive hemicraniectomy in the management of extensive middle cerebral artery stroke: increased survival, at a price

D. J. Blacker and S. Honeybul

1Department of Neurology, Sir Charles Gairdner Hospital, 2The Western Australian Neurosciences Research Institute and 3Department of Neurosurgery, Sir Charles Gairdner Hospital, Royal Perth Hospital and Fiona Stanley Hospital, Perth, Western Australia, Australia
Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke

Future trials
A Multicentre, Randomised Controlled Trial of Exenatide Versus Standard Care in Acute Ischemic Stroke (TEXAIS)

• Hyperglycaemia in acute ischaemic stroke occurs in up to 50% patients, reduces the efficacy of stroke thrombolysis with increased risk of haemorrhage, increases infarct size, and results in worse clinical outcomes and death

• Exenatide is a commonly used diabetes drug (a synthetic glucagon-like peptide-1 receptor agonist) that increases insulin secretion

• Treatment arm will receive Exenatide (Byetta) 5μg subcutaneously twice daily for five days, commencing within 9 hours of symptom onset

• Continuous glucose monitors (CGMs) will track the intra-day dynamic variability of glucose in acute stroke
Practice Patterns for Neurosurgical Utilization and Outcome in Acute Intracerebral Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials 1 and 2 Studies

BACKGROUND: The prognosis in acute spontaneous intracerebral hemorrhage (ICH) is related to hematoma volume, where >30 mL is commonly used to define large ICH as a threshold for neurosurgical decompression but without clear supporting evidence.

OBJECTIVES: To determine the factors associated with large ICH and neurosurgical intervention among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT).

METHODS: We performed pooled analysis of the pilot INTERACT1 (n = 404) and main INTERACT2 (n = 2839) studies of ICH patients (<6 h of onset) with elevated systolic blood pressure (SBP, 150-220 mm Hg) who were randomized to intensive (target SBP < 140 mm Hg) or contemporaneous guideline-recommended (target SBP < 180 mm Hg) management. Neurosurgical intervention data were collected at 7 d postrandomization. Multivariable logistic regression was used to determine associations.

RESULTS: There were 372 (13%) patients with large ICH volume (>30 mL), which was associated with nonresiding in China, nondiabetic status, severe neurological deficit (National Institutes of Health stroke scale (NIHSS) score ≥ 15), lobar location, intraventricular hemorrhage extension, raised leucocyte count, and hyponatremia. Significant predictors of those patients who underwent surgery (226 of 3233 patients overall; 83 of 372 patients with large ICH) were younger age, severe neurological deficit (lower Glasgow coma scale score, and NIHSS score ≥ 15), baseline ICH volume > 30 mL, and intraventricular hemorrhage.

CONCLUSIONS: Early identification of severe ICH, based on age and clinical and imaging parameters, may facilitate neurosurgery and intensive monitoring of patients.

KEYWORDS: Clinical trial, INTERACT, Intracerebral hemorrhage, Neurosurgery, Prognosis
Triple therapy prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT)

• TRIDENT is an international medical research study which aims to determine the effect of more intensive blood pressure control to prevent recurrent stroke in patients who have had an intracerebral haemorrhage

• The aim of this project is to test the superiority of a fixed low-dose combination blood pressure-lowering pill (Triple Pill) strategy in recurrent stroke in patients with a history of ICH

• The TRIDENT Study will be conducted in Australia, the UK, The Netherlands, Sri Lanka, Taiwan, Malaysia and Japan, with expansion to other regions imminent.

• The study aims to recruit 4,200 patients from 150 centres around the world.
TEMPO-2
PI: Prof Shelagh Coutts, University of Calgary

• The primary objective: to demonstrate the efficacy of using TNK-tPA to treat minor ischemic stroke with proven arterial occlusion.
• TIA or minor stroke defined as a baseline NIHSS ≤ 5 at the time of randomization
• Time to treatment time ≤ 12 hours
• Any acute intracranial occlusion or near occlusion in MCA, ACA, PCA, VB territories
• North America, Europe, Asia, Australasia
• Patients will be randomized to single, intravenous bolus (0.25mg/Kg) TNK-tPA or standard of care
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled 42-Day Treatment Study to Evaluate the Effect of DNS-3379 on Upper Extremity Motor Function Following Ischemic Stroke

- DNS-3379 is a selective inhibitor of phosphodiesterase type 4 (PDE4)
- Phase 2a
- Approximately 25 sites in Australia, New Zealand, and North America

**Primary Objectives**
- To assess the efficacy of DNS-3379 versus placebo on upper extremity motor recovery, specifically, sensorimotor function.
- To assess the safety and tolerability of DNS-3379 versus placebo
A Randomized, Double-blind, Placebo-controlled Phase II Multi-Center Investigation to Assess the Safety and Tolerability of DM199 Administered Intravenously and Subcutaneously in Subjects with Acute Ischemic Stroke (DiaMedica study)

• DM199 is a recombinant human version of the KLK1 protein.

• KLK1 has been shown to protect against ischemic brain injury through multiple signalling pathways including anti-inflammation, anti-apoptotic effect, promoting angiogenesis and neurogenesis, and improved cerebral blood flow through vasodilation.

• The objective of this study is to evaluate the safety and tolerability of DM199 in treating subjects presenting with acute ischemic stroke
Intravenous Minocycline in Acute Stroke
A Randomized, Controlled Pilot Study and Meta-analysis

Edith Kohler, MD, FRACP; David A. Prentice, FRACP; Timothy R. Bates, FRACP; Graeme J. Hankey, MD, FRACP; Anne Claxton, BSc; Jolandi van Heerden, FRANZCR; David Blacker, FRACP

Background and Purpose—Minocycline, in animal models and 2 small randomized controlled human trials, is a promising neuroprotective agent in acute stroke. We analyzed the efficacy and safety of intravenous minocycline in acute ischemic and hemorrhagic stroke.

Methods—A multicenter prospective randomized open-label blinded end point evaluation pilot study of minocycline 100 mg administered intravenously, commenced within 24 hours of onset of stroke, and continued 12 hourly for a total of 5 doses, versus no minocycline. All participants received routine stroke care. Primary end point was survival free of handicap (modified Rankin Scale, ≤2) at day 90.

Results—Ninety-five participants were randomized; 47 to minocycline and 48 to no minocycline. In the intention-to-treat population, 29 of 47 (65.9%) allocated minocycline survived free of handicap compared with 33 of 48 (70.2%) allocated no minocycline (rate ratio, 0.94; 95% confidence interval, 0.71–1.25 and odds ratio, 0.73; 95% CI, 0.31–1.71). A meta-analysis of the 3 human trials suggests minocycline may increase the odds of handicap-free survival by 3-fold (odds ratio, 2.99; 95% CI, 1.74–5.16) but there was substantial heterogeneity among the trials.

Conclusions—In this pilot study of a small sample of acute stroke patients, intravenous minocycline was safe but not efficacious. The study was not powered to identify reliably or exclude a modest but clinically important treatment effect of minocycline. Larger trials would improve the precision of the estimates of any treatment effect of minocycline.

Preliminary results of the intravenous minocycline combined with intravenous thrombolysis: A randomized pilot study of a strategy to reduce hemorrhagic transformation in acute ischemic stroke – The West Australian Intravenous Minocycline and TPA Stroke Study (WAIMATSS)
Assessment of the Neuroprotective Effects of Arginine-Rich Protamine Peptides, F--Arginine Peptides, F--Arginine--Tryptophan Peptides, and Arginine--Tryptophan in Vitro Excitotoxicity Occlusion in Rats

Bruno P. Meloni1,2,3, Diego Milan, Adam B. Edwards1,2,4, Ryan S. A., Neville W. Knuckey1,2,3

Received: 12 September 2016 / Accepted: 1
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Research report

Delayed 2-h post-stroke administration of R18 and NA-1 (TAT-NR2B9c) peptides after permanent and/or transient middle cerebral artery occlusion in the rat

Diego Milani1,2,3, Jane L. Cross1,2,3, Ryan S. Anderton4,5, David J. Blacker1,2,3, Neville W. Knuckey1,2,3, Bruno P. Meloni1,2,3

1Perron Institute for Neurological and Translational Science, Nedlands, Australia
2Department of Neurosurgery, Sir Charles Gairdner Hospital, QEII Medical Centre, Nedlands, Western Australia, Australia
3Centre for Neurovascular and Neurological Disorders, The University of Western Australia, Nedlands, Australia
4School of Health Sciences, The University Notre Dame Australia, Fremantle, Western Australia, Australia
5Department of Neurology, Sir Charles Gairdner Hospital, QEII Medical Centre, Nedlands, Western Australia, Australia
A Multicentre, Randomized, Double-blinded, Placebo-controlled, Parallel Group, Single-dose Design to Determine the Efficacy and Safety of Intravenous NA-1 in Subjects with Acute Ischemic Stroke Undergoing Endovascular Thrombectomy (ESCAPE-NA1 Trial)

• The primary objective is to determine the efficacy of the neuroprotectant, NA-1, in reducing global disability in subjects with major acute ischemic stroke (AIS) with a small established infarct core and with good collateral circulation selected for rapid endovascular revascularization.
### The value of trials to Australia

<table>
<thead>
<tr>
<th>Network</th>
<th>Years of operation</th>
<th>Studies</th>
<th>Funding</th>
<th>Publications</th>
<th>Number of trials included</th>
<th>Names of trials included</th>
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</thead>
<tbody>
<tr>
<td>Australasian Stroke Trials Network (ASTN)</td>
<td>19</td>
<td>40 published</td>
<td>&gt;$50m total</td>
<td>180+</td>
<td>7</td>
<td>ARCH, AVERT, ENCHANTED, EXTEND-IA, INTERACT-2, PROGRESS, QASC</td>
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<tr>
<td>Interdisciplinary Maternal and Perinatal Clinical Trials Network (IMPACT)</td>
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<td>147 published</td>
<td>$10-25m total</td>
<td>146</td>
<td>10</td>
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<td>Australian &amp; New Zealand Intensive Care Society Clinical Trials Group</td>
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<td>8</td>
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<td></td>
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<td>28 current</td>
<td>&gt;$10m NHMRC</td>
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Economic evaluation results

If findings from the 25 high impact clinical trials are implemented in 65% of eligible patients seeking treatment in a year:

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<th>Network</th>
<th>Gross benefit</th>
<th>Cost</th>
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<td>$1bn</td>
<td>$106m</td>
<td>9.5:1</td>
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<tr>
<td>IMPACT</td>
<td>$682m</td>
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<td>ANZICS CTG</td>
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<td><strong>$2bn</strong></td>
<td><strong>$336</strong></td>
<td><strong>5.8:1</strong></td>
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</tbody>
</table>

Trial results only need to be implemented in 11% of the eligible patient population for benefits to exceed costs

*As reported in the Profiling Networks Report

Slide courtesy of Julie Bernhardt
Thank you