*FRONTIER-AP: Randomized controlled trial of endovascular versus standard medical therapy for stroke with medium sized vessel occlusion*

**Project Team Roles & Responsibilities**

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**Resources:**

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1. **Project Synopsis**

The distal ischaemic stroke thrombectomy against medical therapy trial is the last FRONTIER in stroke trial. It is an Australian led trial in the AsiaPacific region (FRONTIER-AP) which seeks to answer an important clinical conundrum on the optimal treatment approach for patients with clot in medium sized vessels (MVO) in the brain. Following the results of multiple randomised clinical trials some states in Australia have structured clinical pathways for treatment of patients with large vessel occlusion (LVO)(1). Such knowledge does not yet exist for MVO. There is clinical equipoise to proceed with phase II clinical trial given the conflicting data from multiple observational studies and small sample size of data from randomised clinical trials (2, 3). Our primary hypothesis is that the clinical outcome of ischaemic stroke patients treated with thrombectomy within 9 hours will be superior compared with that of standard medical therapy (alteplase or tenecteplase is approved within 0-4.5 hours, alteplase within 4.5 – 9 hours in Australia but not in all Asian countries). This trial will require moderately large sample (n=240). If the trial shows superiority of thrombectomy for MVO then it may lead to significant restructuring of acute stroke care across multiple states. The trial has been submitted to ANZCTR (ID 382718 submitted on 4/9/21)

1. Background

Prior to 2015, the standard clinical approach for reducing disability and death in ischaemic stroke was Stroke Unit admission, antiplatelet therapy and treatment with recombinant tissue plasminogen activator (TPA) within 4.5 hours from onset in selected patients (1). Subsequently multiple randomised control clinical trials (RCT) have shown effectiveness of endovascular clot retrieval (ECR) or thrombectomy to remove clot from large vessel (involving M1 segment of middle cerebral artery/MCA or proximal M2 segment), as a new and transformative therapy(1). In 2019, Australasian investigators (from the EXTEND family of trials and spearheaded by CI Ma) have shown the TPA is effective up to 9 hours after onset(5). Building on our success in treating large vessel occlusion (LVO) and the lack of clear data, on medium vessel occlusion (MVO) involving segments of the MCA such as M2 or M3 and segments of the anterior cerebral artery/ACA such as A1 or A2, we plan to proceed with trial for MVO. The data are summarised below.

*Data from Registry:* In observational studies, nearly half of the patients with MVO had recanalization with alteplase (6). In a meta-analysis of registry data, recanalisation occurred in 81% (95% CI 79% to 84%). Safety data showed that mortality and symptomatic intracranial haemorrhage rates occurred in 16% (95% CI 11% to 23%) and 10% (95% CI 6% to 16%), respectively(7). In a retrospective analysis of registry data from North America involving 522 patients with M2 clot, the OR was 3.1 (95% CI, 2.1-4.4; P < .001) in favour of thrombectomy(8). However, the two groups differed significantly in terms of age by 6 years (p<0.001)(8). In the German registry data from 2005 to 2020 and involving 169 patients with National Institute of Health Stroke Scale (NIHSS) <5, there was no difference between the two groups in good outcome (defined as modified Rankin Score/mRS 0-2) (2). A subgroup analysis of this data and using a different analysis known as shift Rankin analysis was in favour of thrombectomy over thrombolysis(2). A meta-analysis combining trials and registry data of patients with M2 clot (n=1105) noted good outcome in 58.3% of patients (95% CI 51.7-63.8%) but with symptomatic intracranial haemorrhage of 5.1% (95% CI 4.2-8.3%), and 3-month mortality rate was 12.2% (95% CI 10.4-16.3%)(3). The authors reported high heterogeneity (87.3%) in the data(3). An observational study by our group showed that the outcome was favourable among those with distal occlusions, small infarct core and good collateral and receiving thrombolysis compared to those having thrombectomy (9).

*Data from RCT:* The revised American Heart Association (AHA) guidelines in 2019 stated that “Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS (acute ischaemic stroke) in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.” Examination of the data from the guidelines showed that they had cited 3 papers published in 2016(10-12). The first one came from HERMES collaboration from 5 thrombectomy trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) is in favourable direction compared to medical therapy but the adjusted odds ratio (1.28 [95% CI, 0.51–3.21], n=94) was not significant(10). The SEER collaborators re-evaluated this data but restricted it to patients who were treated with Solitaire stent retriever device. There were only 33 patients in the thrombectomy and 23 in the control group (OR 1.77, 95% CI 0.55-5.65) (11). In the same year, another group evaluated the trials (SWIFT, STAR, DEFUSE2, and IMS3). There were 131 cases of M2, 23 cases of M3 and 6 cases of M4. It was noted that good outcome (Rankin of 0-2) crossed the midline among patients with distal MCA branches (OR 1.4, 95% CI 0.8-2.6). These authors described that, a subset of the distal MCA cohort, reperfusion was associated with excellent functional outcome (OR 2.2, 95% CI 1.0-4.7). It should be noted that the confidence interval touched the midline(12). Our review of these studies suggested that the conclusion in the AHA guidelines in 2019 were perhaps stronger than the available evidence at that time and which was based on very small number of M2 cases.

*Importance of anatomy of M2 in trials and registry:* Definition of proximal and distal M2 segment varies in the literature. The MCA can branch into a superior and inferior M2 trunk with one of the trunks being dominant. The inferior trunk if often straight while the superior trunk makes a downward turn then upward turn. Investigators described better outcome with inferior (66%) compared to superior division occlusion (48%, p=0.04) (13). Some investigators emphasised the role of a dominant M2 (large trunk which continue from M1) as the calibre of the dominant M2 is larger than that for the non-dominant M2. A recent audit from the MRCLEAN registry (M2: n=244) suggested that the outcome is similar between dominant and non-dominant M2(14). In another individual patient meta-analysis of 130 patients from HERMES collaboration, the data was partitioned as 116 cases of proximal and 14 cases of distal M2 or 72 cases of anterior M2 and 58 cases of posterior M2 or dominant M2 in 73 cases, co-dominant in 50 and non-dominant in 7 cases (15). Using the different ways to partition the M2 segment, the authors found that treatment effect was observed with proximal M2 (adjusted OR 2.68, 95% CI 1.13 to 6.37) or dominant M2 but the confidence interval was wide (adjusted OR 4.08, 95% CI 1.08 to 15.48)(15). These efficacy issues are important considerations for planning this trial to evaluate if the efficacy of thrombectomy is higher or lower under trial setting.

*Safety:* Trials and registry data described vessel perforation following stent retriever in 1%(16). The majority (63%) of the cases occurred at distal location. Death followed vessel perforation in 56%. These safety issues are important considerations for planning this trial to evaluate if the complications are higher, similar or lower under trial setting.

*Hypothesis*: We propose that equipoise exists between these 2 diametrically opposed therapeutic strategies, and a study to investigate this question is justified. The rationale of the present study is to determine whether endovascular therapy achieves higher proportion of patients with functional outcomes compared with standard medical therapy.

*Primary Aim-Efficacy*: To test the hypothesis that the proportion of clinical outcome (modified Rankin Scale (mRS) 0-1 or no change from baseline at 3 months if the mRS is 2 at the time of recruitment) in acute ischaemic stroke patients with MCA and ACA branches (M2 or M3 or A2 ) occlusions treated with endovascular therapy within 9 hours is higher than that of standard medical therapy. *Primary Aim-Safety*: To test the hypothesis that thrombectomy for MVO is safe and does not result in increased rate of vessel perforations or symptomatic intracranial haemorrhage.

*Secondary Aim- Efficacy*: To test the hypothesis that thrombectomy for MCA and ACA branches (M2 or M3 or A1 or A2) occlusions results in higher rate of recanalization than current best medical therapy. *Secondary Aim- Health Economics*: To assess the cost-effectiveness of thrombectomy compared to current medical therapy in treating MVO stroke from a healthcare system perspective.

*Tertiary Aim-Operational Research*: Demonstrate feasibility of applying the results of this trial in Phase III via evaluation the effect of intervention on logistics (ambulance transport and hospital crowding) and procedures in hospitals across the states.

1. **Project Design**

**Research project setting:** Centres providing thrombectomy services (Monash Medical Centre, Royal Melbourne Hospital) will provide thrombectomy. Patients can be referred from surrounding hospitals.

**Methodological approach:** The study design is a Bayesian Optimal Phase II (BOP2)[17] multicentre, prospective, randomised, open label, blinded endpoint (PROBE) superiority phase II trial (2 arms with 1:1 randomization) in ischaemic stroke patients within 9 hours of stroke onset. We monitor the efficacy endpoint using the 2-arm Bayesian optimal phase 2 (BOP2) design. The 2-arm BOP2 design is aimed at making go/no-go decisions for two-arm randomised trials. It is flexible, allowing any arbitrary number of interim analyses and it is efficient by maximizing the power of the trial.

*Definition of M2, M3 segments*: The segment of the MCA is defined using the functional anatomy where the segment beyond the origin of the lenticulostriate artery is termed distal MCA (18). In some text, the M2 trunk is defined as the segment of MCA beyond the posterior temporal artery (M2 branch). In this trial we defined the M2 segment as the segment beyond the bifurcation/trifurcation. Following bifurcation/trifurcation of MCA, the M2 trunk continues as M2 division and then M2 branches. *Definition of A1 and A2 segments*: The A1 segment of the anterior cerebral artery originates from the internal carotid artery and communicates with the contralateral hemisphere via the anterior communicating artery. The A2 segment describes the segment of the anterior cerebral artery distal to anterior communicating artery.

**Participants:**

*Inclusion criteria:*

1. Patients presenting with acute ischaemic stroke within 9 hours of stroke onset
2. (NIHSS ≥ 5 or dysphasia if NIHSS <5
3. Pre-stroke modified Rankin Score (mRS) score of 0 or 1 or 2
4. Patient’s age is ≥18 years (or as per local requirements)
5. Endovascular therapy expected to commence (arterial puncture) within 90 minutes of initial non-contrast CT brain.
6. Arterial occlusion on CT Angiography (CTA) or MR Angiography (MRA) of the M2 (proximal, mid or distal), M3, A1, and A2.

*Exclusion criteria:*

1. Patients presenting with acute ischaemic stroke >9 hours of stroke onset
2. Intracranial haemorrhage (ICH) identified by CT or MRI
3. Rapidly improving symptoms at the discretion of the investigator
4. Pre-stroke modified Rankin Score (mRS) score of ≥ 2 (indicating previous disability)
5. Hypodensity in >1/2 MCA or ACA territory on non-contrast CT
6. ICA occlusion ipsilateral to the distal MCA or ACA clot
7. Contraindication to imaging with contrast agents
8. Any terminal illness such that the patient would not be expected to survive more than 1 year.
9. Patients with active cancer and undergoing treatment for cancer are excluded,
10. Any condition that, in the judgment of the investigator, could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
11. Pregnant women

**Participant recruitment strategies and timeframes**: We plan to recruit 1 patients per week and will be recruiting additional sites. We hope to finish recruitment within 5 years.

**Data Collection/Gathering:**

*Imaging Parameters/analysis*: Imaging is performed with CT, CTA and post-contrast CT, or MRI and MRA acutely as part of standard care with imaging follow-up at 24 hours to 48 hours. The sequences and the parameters used follow the STIR (Stroke Imaging Research) roadmap guidelines, but imaging takes place acutely and at 24 to 48 hours only, as previously validated. Sequences may include DWI, MRP, MRA, SWI/T2\* Gradient Echo and FLAIR. *Perfusion mismatch* on CT Perfusion is defined using the approach of EXTEND IV trial(5) (RAPID software, iSchemaView, Menlo Park, CA) or TASTE trial (MIStar software, Apollo Medical Imaging Technology)(19). In brief, infarct core is defined on cerebral blood flow (rCBF) map as <30% of the contralateral side, perfusion deficit as time to maximum of the residue function exceeding 6 seconds(5). The mismatch between the perfusion deficit and infarct core should be greater or equal to 10 ml or a ratio perfusion deficit divided by infarct core as greater or equal to 1.2. The maximum size of the infarct core should be ≤ 70 ml.

*Intervention*: Patients randomised to the thrombectomy arm will have clot extraction by Trevo XP ProVue 3x20mm retriever or “baby Trevo” (Stryker, Neurovascular) or aspiration catheter. The standard care arm is alteplase or tenecteplase within 4.5 hours and between 4.5 - 9 hours, it’s alteplase or tenecteplase or best medical therapy according to the local guidelines. *Post-intervention*: A non-contrast CT and CTA will be performed 24 to 48 hr post intervention. At the investigator’s discretion, a repeat CT Perfusion or MRI may be performed at 24 to 48 hr. For MRI (if used for baseline selection and at 24 to 48hrs), an initial scout view will be followed by isotropic DWI (created from DWI images obtained with diffusion sensitizing gradients applied in 3 orthogonal planes) using b values between 0 sec/mm2, equivalent to a T2-weighted image, and 1000 sec/mm2. Whole brain imaging will use 25 contiguous axial slices each 5 mm in thickness. The imaging time for DWI is approximately 3 minutes. Time of Flight MRA will be obtained to determine the presence or absence of MVO. A T2\*-weighted gradient echo sequence will be performed to assess for presence of ICH. A FLAIR sequence is also acquired. This protocol is identical between the acute and sub-acute (24 h) imaging.

To ensure consistent quality on the imaging-based decision making at the recruiting centres, all imaging data will be electronically transferred and read at the coordinating centreon a weekly basis. The coordinating centre will be kept blinded to the clinical information and will perform the analysis of the radiological outcome measures. Feedback will be provided to individual sites regarding the imaging-based decisions.

The outcome of symptomatic intracerebral haemorrhage (ICH) will be centrally adjudicated by consensus of blinded assessors using the definition ICH (parenchymal haematoma type 2 - PH2 within 36 hours of treatment) combined with neurological deterioration leading to an increase of ≥4 points on the NIHSS from baseline, or the lowest NIHSS value between baseline and 24 hours. The presence of haemorrhagic transformation will be assessed on T2\*-weighted MRI or CT (repeated study within 24 hours or if later clinical deterioration occurs). In those cases where CT Perfusion has been performed, the presence and degree of reperfusion will be determined as the difference between the 24-hour and acute perfusion lesion volumes (percentage change and cm3). Recanalization will be determined based on initial CTA/MRA and 24-hour MRA/CTA and classified according to the TIMI system. Ischaemic core growth is calculated as the absolute and relative difference in volume between CT-rCBF estimated ischaemic core at baseline and 24-hour DWI lesion volume.

**Clinical assessment:** Neurological impairment and functional scores will be measured by a neurologist or health care professional trained in their administration. The assessors will be blinded to the treatment group. The NIHSS is a validated neurological impairment score, which will be performed at baseline, then again at 24 to 48 hours after treatment (or if initially anaesthetised, as soon as assessable). At day 90 (+/- 7 days), the modified Rankin Score (mRS) will be assessed via telephone and adjudicated by a central, blinded panel to assess functional outcome.(20) An improvement in the NIHSS of ≥ 8 or final NIHSS ≤ 1 and an mRS of 0 or 1 (or mRS 2 if the premorbid mRS is 2) are used as indicators of good or excellent outcome.

Details of the study visit will be described in the protocol paper. In summary, ***Clinical assessments:*** NIHSS and pre-stroke mRS recorded in clinical notes upon presentation to hospital will be recorded in the CRF as baseline measurements. Results of the baseline physical examination will also be recorded, as well as past medical history and stroke details and history. ***Imaging:*** Patients will have standardised multimodal CT or MR prior to treatment. ***Medical history, concomitant medications & Electrocardiograph (ECG):*** Details of patients’ medical history (including stroke history) and anti-platelet concomitant medications will be recorded. Results of ECG performed as part of standard care will be recorded if available. ***Blood collection:*** Results from standard care blood tests performed at screening will be recorded (Routine haematology, biochemistry and coagulation screening tests. Study schedule of assessments). ***Randomization:*** Patients eligible for the RCT based on large vessel occlusion and eligibility for thrombolysis will be randomised in the ratio 1:1 to receive either endovascular therapy or standard medical therapy according to a centralised web-based procedure. Patients who are not eligible for treatment will be entered as screening failures in the Screening Log (Table 1).

**Treatment *Endovascular therapy:*** All patients will be transferred to the interventional neuroradiology suite with an emphasis on minimising delays to groin puncture. If dramatic clinical recovery occurs in the interim, the patient should still undergo diagnostic angiography. Our experience from previous thrombectomy trials is that these patients may still have residual clot and can deteriorate. Recovery does not necessarily imply recanalization and angiography is the best method to establish whether there is an ongoing target for therapy. The use of conscious sedation or general anaesthesia for the procedure will be at the investigator’s discretion. Close attention should be paid to maintaining stable blood pressure and minimising delays in starting the procedure. During the procedure, catheters may be flushed with heparinised saline at a concentration of 1000 unit heparin per 1.0 L 0.9% sodium chloride. Mechanical thrombectomy as standard of care procedure, will be with stent retriever device as first line intervention. The decision for proximal balloon guide and aspiration, distal intermediate catheter aspiration or subsequent use of additional catheters or devices is at the discretion of the investigator. Stenting of the extra-cranial internal carotid artery or intracranial atherosclerotic disease is permitted when absolutely necessary to obtain access to distal occlusion or to prevent acute re-occlusion. This may require the use of antiplatelets. Otherwise, no heparin or antiplatelets/anticoagulants should be given until at least 24 hours after the procedure. The initial and final angiograms will be centrally graded for angiographic reperfusion using the modified Treatment In Cerebral Ischaemia (mTICI) score (21) and any embolisation into new territories. In addition, presence of intracranial atherosclerotic disease will be quantified. Close neurological observation will be conducted primarily during the first 48 hours after treatment administration according to local clinical practice.

***Day 1 (18- 30- hour) Imaging:*** All patients will have non-contrast CT or multimodal MR or CT Perfusion at investigator’s discretion at 24 to 48 hours post treatment to assess reperfusion, recanalization, ischaemic core growth and haemorrhagic transformation. Some form of reperfusion assessment (MR or CT) is optimal for the trial outcome. ***Clinical assessments:*** Neurological assessment (NIHSS) will be performed at 24 to 48 hr. or, if the patient is anaesthetised, as soon as practicable after 24 hrs by a blinded health professional.

***Day 3 Clinical assessments:*** Neurological and functional assessment by NIHSS will be performed by a blinded health professional. Information on stroke recurrence and hospital readmissions will be collected. Discharge date and destination will be recorded. ***Demographic information and concomitant medications***: Prior to patient discharge, demographic information and anti-platelet concomitant medications will be recorded. ***Day 90 Clinical assessments:*** A trained health care professional will assess the mRS via telephone interview with the transcript assessed by multiple blinded readers to achieve a consensus rating.(20) Anti-platelet concomitant medications and “home time”(22) will be recorded.

***Adverse Events (AE):*** All patients will be asked about adverse events. Adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Serious adverse events (SAE)** is defined as any untoward effect such as death, life threatening, requires prolonged hospitalisation (for inpatients) or requires further intervention to prevent permanent damage or unplanned hospital readmissions

or results in disability/incapacity

***Study restrictions*:** Administration of intravenous heparin, antiplatelet drugs, oral anticoagulants and other unproven therapies will be prohibited in the first 24 hours. However, patients will not be excluded from any treatments as indicated by best medical practice according to the discretion of their treating clinician.

**Data Management:**

Data will be kept in secure location for 7 years or as required by Ethics Committee.

***Statistical analysis, Sample size and stopping rule***: We monitor the efficacy endpoint using the 2-arm Bayesian optimal phase 2 (BOP2) (17) design. Specifically, let $n$ denote the interim sample size and $N$ denote the maximum sample size. Let $p\_{con}$ denote the probability of response in control treatment, $p\_{exp}$ denote the probability of response in experimental treatment. We define the null hypothesis $H\_{0}:p\_{exp}\leq p\_{con}$ , under which the experimental arm is deemed as unacceptable, with respective to the control. We employ the following Bayesian rule to make a go/no-go decision:

* (**Futility stopping**) stop enrolling patients and claim that the experimental arm is unacceptable if

$$Pr(p\_{exp}>p\_{con}|data)<λ(\frac{n}{N})^{α},$$

* (**Superiority stopping**) stop enrolling patients and claim that the experimental arm is acceptable if

$$Pr(p\_{exp}>p\_{con}|data)>2Φ(Z\_{(1+λ)/2}\sqrt{\frac{n}{N}})-1,$$

* where $λ$=0.96 and $α$=0.94 are design parameters optimised to maximize the power under $H\_{1}:p\_{con}$ = 0.4 and $p\_{exp}$ = 0.6, while controlling the type I error rate at 0.05 under $p\_{con}$ = $p\_{exp}$ = 0.4. This optimization is performed assuming a vague prior Beta (0.4,0.6) for $p\_{con}$ and a vague prior Beta (0.6,0.4) for $p\_{con}$. The above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.91

We will perform the interim analysis when the number of enrolled patients reaches 60, 120, 180. When the total number of patients reaches the maximum sample size of 240, we reject the null hypothesis and conclude that the experimental arm is acceptable, compared to the control, if the futility stopping boundary is not crossed. Specific stopping boundaries for futility and superiority are generated for each interim analysis depending on the number of observed responses in control group. For example, for the interim analysis at 90 control participants and 90 intervention participants, if the observed number of control participants with positive outcome is 15-16, the trial can be stopped for futility if the corresponding number in treatment arm is 18 or below, while stopping for superiority can happen if this number is 29 or above. This design exhibits the following operational characteristics on 10,000 simulations using the BOP2 web application: the probability of early stopping of 0.78 (for futility: 0.03; for superiority: 0.75) with average sample size of 171. The proportions of participants with positive outcome will be used as inputs for the decision to declare futility, superiority, or acceptability of the intervention compared to control that will be based on the Bayesian decision rules specified above in the trial design section.

***Trial Management (Steering) Committee*:** The committee will consist of CIs from this grant and is separate from the Data and Safety Monitoring Board. The committee will meet monthly to review trial recruitment, trial conduct, safety and scientific conduct of trial described in the section C (Milestone and Performance Indicators) and E2 (Risk management plan). ***Data and Safety Monitoring Board (DSMB):***The DSMB will be comprised of two physicians with experience in clinical trials and have served as members of DSMB. The members of this committee are not involved in the trial or part of the trial management committee.

**Table 1: Schedule of Assessment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Investigation | Day 0 | Day 1 | Day 3 | Day 90 | Interim Analysis |
| Imaging | CT/CTA± Perfusion | CT/CTA or MRI/MRA | No | No |  |
| NIHSS | Yes | Yes | Yes | Yes |  |
| mRS | Yes (pre-morbid) | No | No | Yes (phone/video) |  |
| ECG | Yes  | Yes  | No | No |  |
| Routine bloods | Yes | Yes | No | No |  |
| Screen log | Yes | No | No | No |  |
| Thrombectomy | Randomised | No | No | No | N=60 |
| Thrombectomy | Randomised | No | No | No | N=120 |
| Thrombectomy | Randomised | No | No | No | N=180 |
| Thrombectomy | Randomised | No | No | No | N=240 |

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