Cerebrovascular Diseases

Protocols

Cerebrovasc Dis
DOI: 10.1159/000534706

Received: June 14, 2023
Accepted: September 22, 2023
Published online: October 26, 2023

The main Optimal Post rTpa-Iv Monitoring in Ischemic Stroke Trial (OPTIMISTmain): Protocol for a Pragmatic, Stepped Wedge, Cluster Randomized Controlled Trial

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Keywords
Ischemic stroke · Thrombolysis · Acute care · Health systems · Nursing care

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A complete list of sites and trial investigators and coordinators is provided in the Supplementary Material.
Trial registration: Clinicaltrials.gov (NCT03734640) and ANZCTR (ACTRN 12619001556134p).

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Abstract

Introduction: Careful monitoring of patients who receive intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) is resource-intensive, and potentially less relevant in those with mild degrees of neurological impairment who are at low risk of symptomatic intracerebral hemorrhage (sICH) and other complications. ***Methods:*** OPTIMISTmain is an international, multicenter, prospective, stepped wedge, cluster randomized, blinded outcome assessed trial aims to determine whether a less-intensity monitoring protocol is at least as effective, safe, and efficient as standard post-IVT monitoring in patients with mild deficits post-AIS. Clinically stable adult patients with mild AIS (defined by a NIHSS <10) who do not require intensive care within 2 h post-IVT are recruited at hospitals in Australia, Chile, China, Malaysia, Mexico, UK, USA, and Vietnam. An average of 15 patients recruited per period (overall 60 patient participants) at 120 sites for a total of 7,200 IVT-treated AIS patients will provide 90% power (one-sided α 0.025). The initiation of eligible hospitals is based on a rolling process whenever ready, stratified by country. Hospitals are randomly allocated using permuted blocks into 3 sequences of implementation, stratified by country and the projected number of patients to be recruited over 12 months. These sequences have four periods that dictate the order in which they are to switch from control (usual care) to intervention (implementation of low intensity monitoring protocol) to different clusters of patients in a stepped manner. Compared to standard monitoring, the low-intensity monitoring protocol includes assessments of neurological and vital signs every 15 min for 2 h, 2 hourly (vs. every 30 min) for 8 h, and 4 hourly (vs. every 1 h) until 24 h, post-IVT. The primary outcome measure is functional recovery, defined by the modified Rankin scale (mRS) at 90 days, a seven-point ordinal scale (0 [no residual symptom] to 6 [death]). Secondary outcomes include death or dependency, length of hospital stay, and health-related quality of life, sICH, and serious adverse events. ***Conclusion:*** OPTIMISTmain will provide level I evidence for the safety and effectiveness of a low-intensity post-IVT monitoring protocol in patients with mild severity of AIS.

Introduction

Acute ischemic stroke (AIS) is a major global disease burden, with intravenous thrombolysis (IVT) using alteplase, and increasingly tenecteplase, being the mainstay of reperfusion treatment [1]. As post-IVT AIS patients are at high-risk of neurological deterioration and treatment-related complications (e.g., symptomatic intracranial hemorrhage [sICH]) [1], guidelines recommend that they receive close monitoring of vital signs and neurological function every 15 min for the first 2 h, every 30 min for the next 6 h, and then every hour until 24 h [2]. This typically requires patients to be managed in a monitored area such as stroke unit or in some cases, an intensive care unit, but sICH and other complications are infrequent in patients with mild neurological deficits [3, 4]. The single-center, open-label, single-arm, Optimal Post rTpa-Iv Monitoring in Ischemic Stroke Trial (OPTIMIST, NCT02039375) feasibility study suggested that patients with mild AIS do not need intensive post-IVT care [5]. We outline the protocol for OPTIMISTmain study which aims to determine whether low-intensity monitoring is “non-inferior,” safe, and resource efficient, as compared to standard post-IVT AIS monitoring. Herein, we report the final version of the trial protocol, compliant with the Stepped Wedge extension of the Consolidated Standards Of Reporting Trials (CONSORT) [6] reporting guideline (online suppl. Material S1; for all online suppl. material, see https://doi.org/10.1159/000534706).

Methods

Design

OPTIMISTmain is a pragmatic, multicenter, prospective, stepped wedge, blinded outcome assessed, cluster randomized controlled clinical trial. Sites (hospitals) are randomly allocated to 3 sequences, to recruit patients across 4 steps from control (standard monitoring) to the random allocation of crossover to intervention (Fig. 1). The design has used a mixed consent process, which including written informed consent from a cluster guardian (an appropriate senior delegate) to implement the intervention as usual care (except US due to ethics requirement) and individual standard written informed consent for the collection of data during the hospital stay and follow-up. The mixed consent approach offers several advantages: avoidance of contamination of the intervention across patient groups; facilitates the implementation of the intervention within routine practice; and achieves the large sample size required to determine the treatment effect on patient-centered outcomes.

Patient Population

Eligible AIS patients (age ≥18 years) are those who receive IVT according to guideline criteria, are stable (blood pressure [BP] ≤180/105 mm Hg) with mild neurological impairment (National Institute of Health Stroke Scale [NIHSS] <10), 2 h post-IVT infusion and can be managed on an appropriate monitoring ward (detailed in online suppl. Material S2). Each participating site will record all AIS stroke patients given IVT and who meet eligibility criteria during the study recruitment period using the Screening and Enrolment log to ensure consecutive recruitment.

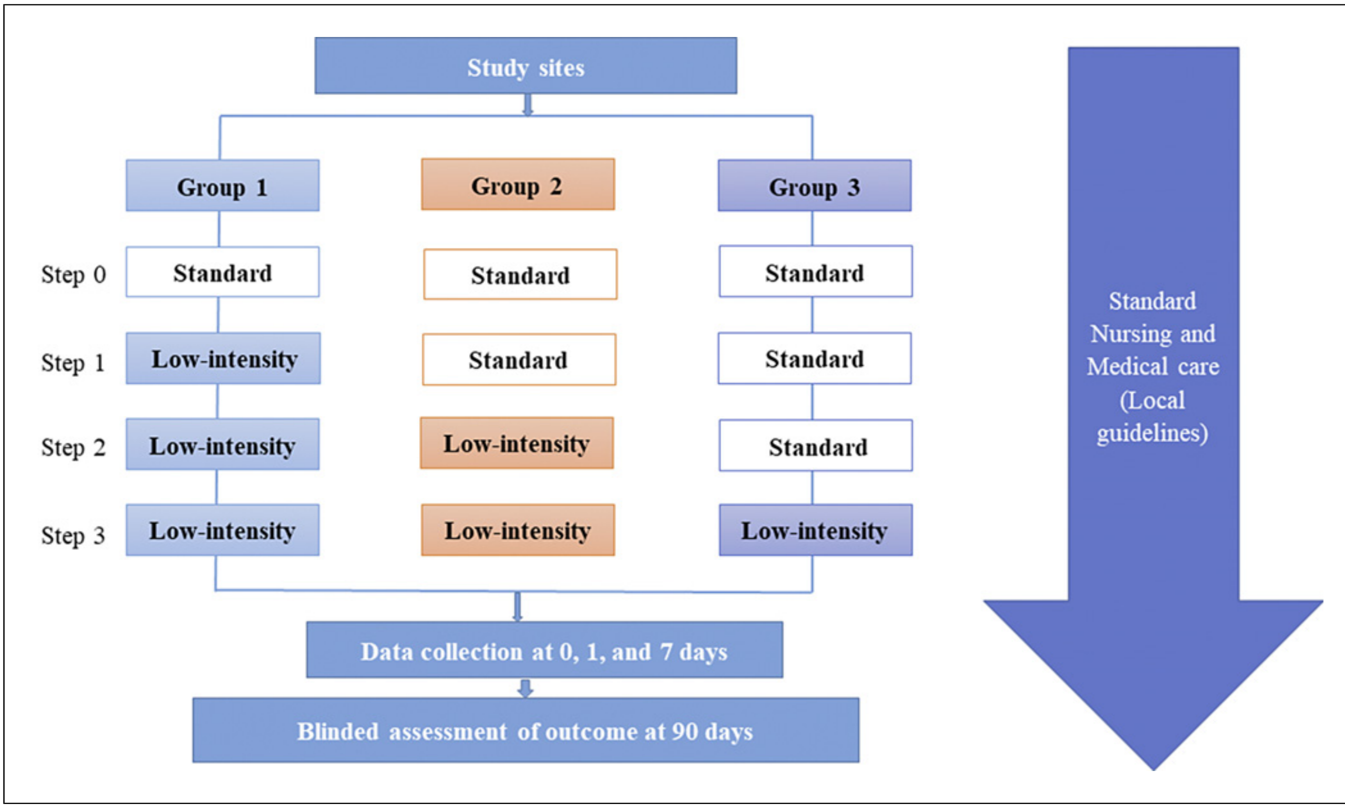

Fig. 1. OPTIMISTmain Trial schema. All sites (hospitals) are randomly allocated to one of three groups (groups 1, 2, or 3) in which patients are recruited across four timing phases ("steps"), with the period of each step defined by a set timeframe (4 months). For example, sites allocated to group 1 will enroll every eligible patient in standard of care monitoring (control) for at least 4 months, this is followed by 12 months of enrolling patients and monitoring at a low-intensity frequency (intervention). Group 2 will have 8 months of standard of care and 8 months of low-intensity frequency of monitoring.

Randomization

The unit of randomization is the site, randomly assigned by an unblinded statistician not otherwise involved in the study. Sites are randomized into one of three treatment sequences using a pre-specified randomization schedule with permuted blocks of participating sites and the estimated recruitment capacity (number of patients <60 or ≥60), stratified by country. Sites are notified of their sequence within 2 weeks of an agreed start date after which they are required to consecutively enroll eligible post-IVT AIS patients.

Interventions

Low-intensity monitoring (intervention) – vital signs (heart rate [HR], BP) and neurological assessment (Glasgow coma scale [GCS] and/or NIHSS, according to local protocols) every 15 min for 2 h, 2 hourly for 8 h, and 4 hourly until 24 h, post-IVT (Fig. 2).

Standard monitoring (control) – vital signs (HR, BP) and neurological assessment (GCS, NIHSS) every 15 min for 2 h, every 30 min for 6 h, and hourly until 24 h, post-IVT (online suppl. Material S3).

Other management is according to usual standards of care.

Discontinuation of the Monitoring Strategy

The principal investigator (PI) must not deviate from the monitoring strategy except when there is a contraindication due to a patient's condition. Low-intensity monitoring should be discontinued if any of the following occurs: 1) a serious adverse event (SAE), which in the opinion of the investigator is related to the study protocol; or 2) the investigator feels it is in the patient's best interest.

Outcomes

The primary outcome is the modified Rankin scale (mRS) at 90 days, which is an ordinal 7-point scale (0 [no residual symptom] to 6 [death]) assessed by a trained clinician, blind to treatment allocation. Secondary outcomes include: reported symptomatic intracranial hemorrhage (sICH) according to Heidelberg criteria [7]; time (hours) to request presumed sICH neuroimaging from last monitoring; neurological deterioration (i.e., shift in NIHSS scores at 7 days, or at hospital discharge if earlier); death or dependency (mRS 2–6) at 90 days; death within 90 days; length of hospital stay (<7 or ≥7 days); health-related quality of life using the 5-level EuroQoL Group 5-Dimension self-report questionnaire (EQ-5D-5L) [8]; SAEs within 90 days, reviewed centrally with

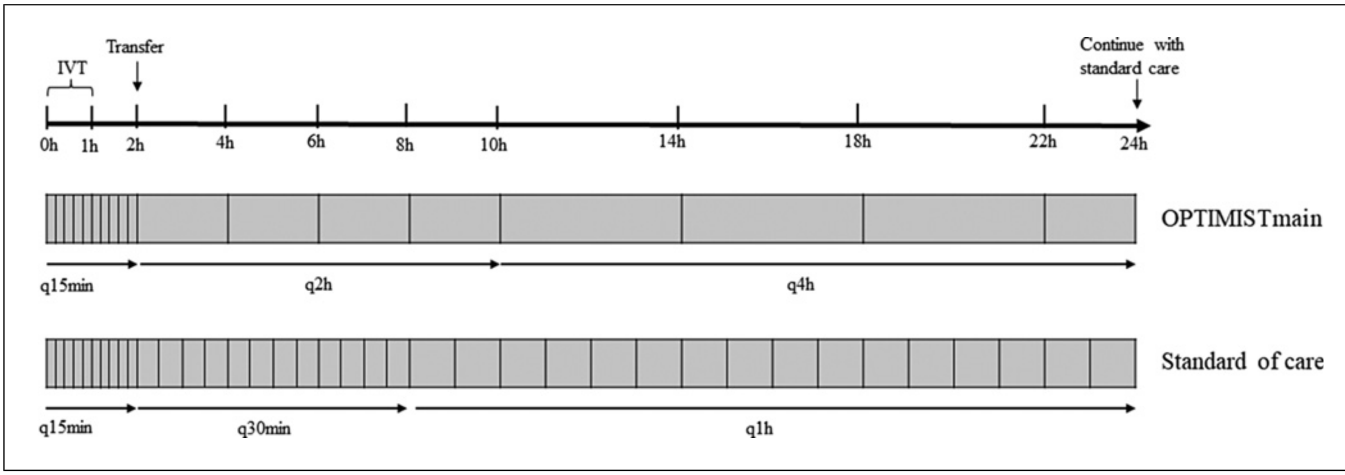

Fig. 2. OPTIMISTmain monitoring care compared to standard of care. IVT denotes intravenous thrombolysis.

standard criteria; and Patient Reported Experience Measurement (PREMs) [9] and sleep-related impairment [10] within 7 days (except in the USA), conducted by a trained assessor blind to intervention. A process evaluation will assess implementation outcomes of low-intensity monitoring and features of the intervention that may have met with resistance. The impact of organizational changes that are a result of the COVID-19 pandemic are assessed as contextual factors in relation to infection control, ward layout, staffing resources, patient admissions, and use of personal protective equipment (PPE) at each site, and at three discrete timepoints: baseline (prior to enrolling patients), when crossing over to intervention, and at the end of study (cessation of enrolment). Economic indicator data, including of health services and hospital readmissions within 3 months, will allow future cost-minimization analysis. Details of process evaluation and economic evaluation are described in online supplementary Material (S4).

Safety Monitoring

All SAEs are required to be reported to central coordinating center (CCC) within 24 h of the site study team first becoming aware of the event by reporting the event in the case report forms in the study database. SAEs are also required to be reported by the site investigator to the relevant human Ethics Committee in accordance with and within the timeframe specified in relevant guidelines. Details of the SAE will include the event diagnosis, classification of the event using the above definitions, the PI's opinion on the causal relationship to the randomized monitoring strategy, and the timing of the event. The PI will be responsible to ensure all investigators follow-up the event until the outcome of the SAE is finalized. The CCC will closely monitor all SAEs for any relationship to the study procedures and protocol, or any clustering of events at a particular site. The protocol may be amended or the study stopped early, if an excess of a particular SAE appears to be protocol-related. An independent data and safety monitoring board reviews safety and outcomes approximately every 6 months, according to relevant guidelines and regulations. The CCC will submit all SAEs to the data safety monitoring board for regular review and if needed, outside of the planned safety and interim analysis meetings. Since patients with AIS are often unstable and can deteriorate, and IVT has potential harms, the most serious being sICH. For this reason, specific questions regarding the adverse event of special interest, that of sICH, will be collected should a participant experience such an event. Regional Coordinating Centers facilitate translation and adherence of the protocol (online suppl. Material S5).

Sample Size

The use of IVT has been shown to increase the odds of an excellent outcome (mRS scores 0–1) compared to control (36.7% vs. 29.1%) with an odds ratio (OR) of 1.43 (95% confidence interval [CI] 1.23–1.65) or relative risk (RR) of 1.26 (95% CI: 1.15–1.40) [11]. We chose the lower 95% CI boundary of anticipated treatment of IVT to establish the non-inferiority margin to correspond to loss of efficacy of IVT from low-intensity monitoring, assuming patients in the usual care group will experience a similar rate of good outcome (mRS 0–1) (48.9%) to the standard-dose IVT arm in another international trial [12]. Assuming the non-inferiority margin is 1.15, a conventional, individual randomized, trial involving 1,868 AIS patients would provide 90% power (one-sided α 0.025) to show non-inferiority (42.5% good outcome). The stepped-wedge cluster randomized design requires 120 hospitals (3 sequences/4 periods), each recruiting an average of 15 patients per period, for a total of 7,200 participants, and assuming 10% missing primary outcome, 5% nonadherence, and an interclass correlation coefficient of 0.044 from a previous international cluster randomized study [13]. Given the non-inferiority hypothesis, this sample size calculation is based on a dichotomous analysis of mRS (scores of 0–1 vs. 2–6); whilst the main analysis will consist of an ordinal analysis. The assumption is that the ordinal analysis will provide at least as much power as the dichotomous approach by using the full distribution.

Statistical Analysis

All analyses will be undertaken at the patient level with adjustment for clustering by hospital. The main analysis will be performed on a modified intention-to-treat basis by including all participants who provide written consent and have primary outcome data available, regardless of protocol adherence. The non-inferiority effect will be tested through a prespecified non-inferior margin of relative risk of 1.15; if non-inferiority is established, the results will then be tested for superiority. The primary analysis of mRS at 90 days will be performed using an ordinal logistic regression assuming proportional odds and with the effect of the intervention (low-intensity monitoring vs. standard monitoring care) estimated as the common OR of a better outcome (a "positive shift" in mRS scores). The logistic model will include a fixed effect of time, a fixed effect indicating the intervention assignment at each timepoint, and a random site effect to account for clustering. A blind review of the data will be performed to determine the optimal approach for modelling time trends (online suppl. Material S6 for additional details). A detailed statistical analysis plan will be developed prior to unblinding and made publicly available.

Trial Status

The study commenced in the USA in April 2021; and in other countries from August 2021. Recruitment of hospitals and patients is ongoing to achieve the projected targeted sample size (online suppl. Table S1) and the study is anticipated to be completed by November 2024. Investigators have been receptive to participating as a way of reallocating limited resources during the COVID pandemic, but their start-up was often delayed by reduced research capacity. To respond to the COVID-19 pandemic, site training and activation have been performed remotely via teleconference (Teams/Zoom), with video trainings placed on a website platform for ready access by study team members. Weekly remote checks of the data entered was performed centrally by the study team, with an immediate teleconference call held in case of issues are detected. Due to the impact of COVID on staff resources in stroke and other services, timelines for the activations of sites were extended. In USA, a lengthening of each step for ~7 months in 13/20 sites to facilitate the enrolment to reach the target number for the trial had been reported to the data safety monitoring board by Steering Committee. In addition, relevant information is collected through a Hospital Organisation Questionnaire (online suppl. Material S7) to measure the impact of the COVID-19 pandemic and corrective measures taken at three timepoints: at site initiation, transfer to intervention, and at close out.

As of March 20, 2023, 1,334 patients have been included from 41 hospital sites worldwide, including in the USA, Chile, Australia, Malaysia, and the UK Table 1 shows the profile of enrolled patients, with a mean age 65.3 (SD 15.3) years, 53.5% male, and 60.1% Caucasian. Overall, 56.9% had their immediate post-IVT care outside of ICU and 98.2% were considered stable with improving neurological status at baseline. Most participants had a history of hypertension (66.5%), followed by hypercholesterolemia (42.8%), diabetes mellitus (27.2%), and coronary heart disease (19.5%). Grouped median (IQR) NIHSS scores were 5 (3–7), 2 (1–5), 1 (0–3), and 1 (0–2) at baseline, immediately post-IVT, and at 24 h and 7 days post-IVT, respectively. Table 2 describes the pooled outcomes to date. Only 3.3% of the participants had any ICH, of which 0.8% had associated major neurological deterioration. Of 914 participants with complete 90-day follow-up, all-cause mortality was 2.3%, and death or major disability (mRS 3–6) was 19.0%.

Discussion

OPTIMISTmain may provide the evidence necessary to support safe improvement in the management of health care resources, which has been a critical issue during the COVID-19 pandemic: how to maintain health services when facing major tightening of constraints in terms of hospital beds and skilled nursing. Intensive post-IVT monitoring is challenging access to ICU beds and when there is reduced capacity for skilled nursing. Since low-intensity monitoring can free up time in relation to reduced monitoring, our intervention offers the potential for a shift in resources toward more direct care and education by nursing staff, as well as in freeing up the utilization of ICU beds for other patients. Patients may feel better from having less disruption to their sleep from reduced monitoring, and this in turn may improve their recovery and consequently shorten hospital length of stay.

Preliminary data shed light on patient characteristics, feasibility, and safety, of our trial, although these data might be different in the final results. In comparison to the feasibility study [6], the characteristics of patients enrolled in this international multicenter trial are older and have greater neurological severity, but with improvement in their NIHSS profile from 24 h to day 7. Compared to post-IVT sICH rates of 5.2–5.9% reported in open-labeled studies and pooled analysis of RCTs [14, 15], and fatal ICH of 2.9% for those with mild AIS (NIHSS scores <10) [4], the low rates of sICH (3.3%) and death (2.3%) reported in OPTIMISTmain to date suggest the intervention monitoring protocol is feasible and safe. As more than half of the patients were cared outside of the ICU immediately after receiving IVT, the intervention also supports the potential for it to be a cost-effective alternative to the use of current resources which remain stretched in the shadow of the COVID-pandemic.

The stepped wedge cluster randomized control design offers some efficiency gains for implementing complex

Table 1. Characteristics of patients enrolled in OPTIMISTmain, as of March 20, 2023

Characteristics	Data (N = 1,303)
Age, year (N = 1,285)	65.3 (15.3)
Male	688/1,286 (53.5)
Ethnicity race[a]	
Black	146/1,285 (11.4)
Asian	50/1,285 (3.9)
Hispanic	285/1,285 (22.2)
White/Caucasian	772/1,285 (60.1)
Indigenous	4/1,285 (0.3)
Uncertain or other	28/1,285 (2.2)
Systolic blood pressure, mm Hg (N = 1,281)	153.2 (24.7)
Diastolic blood pressure, mm Hg (N = 1,281)	86.0 (15.2)
NIHSS on arrival (N = 1,282)	5 (3–7)
GCS on arrival (N = 1,139)	15 (15–15)
Premorbid according to mRS grade 0-1	1,120/1,283 (87.3)
Undertaking endovascular treatment	37/1,283 (2.9)
Neurological status	
Stable	644/1,281 (50.3)
Improving	613/1,281 (47.9)
Worse but not requiring critical care	22/1,281 (1.7)
Worse and requiring ICU care	2/1,281 (0.2)
Medical history	
Previous ischemic stroke	227/1,284 (17.7)
Previous intracerebral hemorrhage	9/1,284 (0.7)
Coronary heart disease	251/1,284 (19.5)
Atrial fibrillation	127/1,284 (9.9)
Other heart disease	173/1,284 (13.5)
Hypertension	854/1,284 (66.5)
Diabetes mellitus	349/1,284 (27.2)
Hypercholesterolemia	550/1,284 (42.8)
Thrombolytic agent used	
Alteplase	984/1,289 (76.3)
Tenecteplase	304/1,289 (23.6)
NIHSS score after thrombolysis	2.0 (1.0–5.0)
Location of immediate post-thrombolysis care	
Acute stroke unit	414/1,290 (32.1)
Intensive care unit	556/1,290 (43.1)
Intermediate/step down/high dependence care unit	135/1,290 (10.5)
Other	185/1,290 (14.3)

Data are mean (±SD), median (IQR), frequency (%). AIS, acute ischemic stroke, GCS Glasgow coma scale, ICH intracerebral hemorrhage, ICU intensive care unit, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale. [a]Black includes African American, and of African origins; Asian includes Far East, South East Asian, and Indian subcontinent; Hispanic includes Latin America and Spanish; White/Caucasian includes European, Middle East, and North Africa; indigenous includes Aboriginal, Pacific Islander, and Native Hawaiian.

interventions and avoiding contamination. However, it is prone to confounding from secular changes to background processes of care, as has occurred during COVID. In the final statistical analysis model, we will take account of the effect of time, either as a categorical effect representing the study period or as calendar time according to a blind review of start and stop times for each period and each site. This was a lesson learnt from the recently completed third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3), which used a similar stepped wedged design [16]. We have purposely incorporated activities to collect process of care data associated with COVID for future analyses. Undertaking the study across a range of

Table 2. Pooled outcomes of interests in patients enrolled in OPTIMISTmain

Outcomes	Data (*N* = 1,303)
Day 1	
NIHSS score at day 1 (*N* = 1,244)	1 (0–3)
Neurologically stable or improved	1,251/1,291 (96.9)
Intracerebral hemorrhage	31/1,289 (2.4)
Day 7	
NIHSS score at day 7 (*N* = 1,292)	1 (0–2)
Presumed final stroke diagnosis	936/1,235 (75.8)
Large vessel atheroma (>50% stenosis) in extra- or intra-cranial vessel	132/934 (14.1)
Small vessel or perforating vessel lacunar disease	198/934 (21.2)
Cardio-emboli	266/934 (28.5)
Dissection	13/934 (1.4)
Uncertain etiology	288/934 (30.8)
Other definite pathological mechanism	37/934 (4.0)
Day 90	
All-cause mortality	21/914 (2.3)
Death or major disability (mRS 3–6)	174/914 (19.0)
Any reported SAEs	227/1,303 (17.4)
Any reported ICH events	43/1,303 (3.3)
Associated with major neurological deterioration	11 11/1,303 (0.8)
Associated with minor neurological deterioration	4 4/1,303 (0.3)

Data are mean (±SD), median (IQR), frequency (%). AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SAE, serious adverse event.

health care settings enhances the opportunity for the results to have wide applicability and influence on clinical practice.

Concern may be expressed over our choice of non-inferiority margin for the primary outcome and in using the shift in scores on the mRS instead of the conventional binary outcome of mRS 0-1. Another concern may be that low-intensity monitoring care might delay the detection and management of sICH, delirium, and falls, despite being infrequent in our target AIS patient subpopulation. Any SAEs or discontinuation of care will be closely monitored to better understand the adverse consequences of less-intense care. Since patients who are ineligible (NIHSS score >10 or other intensive care requirements) are also admitted during the study period, stroke units or monitoring departments might incorporate separate protocols for patients with the use of IVT during the intervention period. Any concerns of contamination by having mixed implementation of separate protocols in relation to participation in OPTIMISTmain study will be reduced by appropriate labelling of OPTIMISTmain trial patients from others. We will also explore the challenges of integrating the less-intense monitoring protocol into routine practice through the conduct of a process evaluation alongside the trial. We acknowledge that a limitation of this work is that low-intensity monitoring care may not be generalizable to all AIS patients, and especially those with greater neurological severity. We believe, however, that our study will be able to provide high-quality evidence to guide the clinical management of minor AIS patients, with improvement in economic and resource allocation, relative to standard monitoring. In summary, OPTIMISTmain is on schedule to provide level I evidence for low-intensity monitoring for mild post-IVT AIS patients, whilst also allowing analyses of economic and resource benefits, relative to standard monitoring.

Statement of Ethics

This study protocol was reviewed and approved by Sydney Local Health District (RPAH) Ethics Review Committee, approval number X20-0014. Each participating site must obtain written approval(s) from their hospital research Ethics Committee (EC) (e.g., Institutional Review Board [IRB]), and any other relevant regional or national body, before patient recruitment commences. A variable, mixed informed consent process is used, according to local/national rules and regulations: (1) cluster guardian consent or appropriate approval (e.g., signed by the General Manager or Chief Executive of the hospital, or Head of Neurology/Neurosurgery/Stroke Department) for patients to receive the low-intensity monitoring to be implemented for eligible patients in the Stroke Unit, Intensive Care Unit, or Neurology/Neurosurgery Wards; and (2) use of individual standard consent for the collection of data through in-person assessment and data extraction from medical records during the hospital stay and routine follow-up. Written informed consent was obtained for participation in this study.

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Sources

Funding has been received from the National Health and Medical Research Council (NHMRC) of Australia; New South Wales Health Investigator Development Grant, UNSW Medicine noncommunicable diseases theme E/MCR Seed Grant Scheme, the Medical Research Future Fund (MRFF, ID F02176) for conduct in Australia; and Genentech, Inc. for conduct in the USA.

Author Contributions

Menglu Ouyang wrote the first draft of the manuscript, with input from Roland Faigle, Xia Wang, Victor C. Urrutia, and Craig S. Anderson. Laurent Billot contributed to the statistical analysis and sample size calculation. Hueiming Liu and Stephen Jan contributed to the methodology of process evaluation and economic evaluation. Brenda Johnson, Debbie Summers, Pooja Khatri, Alejandra Malavera, Paula Munoz Venturelli, Francisca González, Francisca Urrutia, Diana Day, Lili Song, Yi Sui, Candice Delcourt, Thompson G Robinson, Alice Durham, Ahtasam Ebraimo, Wan Asyraf Wan Zaidi, and Richard I Lindley provided comments on the study design and responsible for trial data collection and quality control procedures. All authors reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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