

World Stroke Organization Brain & hEart globAI iniTiative Program

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Keywords

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Abstract

Introduction: The World Stroke Organization (WSO) Brain & Heart Task Force developed the Brain & hEart globAl initiative (BEAT), a pilot feasibility implementation program to establish clinical collaborations between cardiologists and stroke physicians who work at large healthcare facilities.

Methods: The WSO BEAT pilot project focused on atrial fibrillation (AF) and patent foramen ovale (PFO) detection and management, and poststroke cardiovascular complications known as the stroke-heart syndrome. The program included 10 sites from 8 countries: Brazil, China, Egypt, Germany, Japan, Mexico, Romania, and the USA. The primary composite feasibility outcome was the achievement of the following 3 implementation metrics (1) developing site-specific clinical pathways for the diagnosis and management of AF, PFO, and the stroke-heart syndrome; (2) establishing regular Neurocardiology rounds (e.g., monthly); and (3) incorporating a cardiologist to the stroke team. The secondary objectives were (1) to identify implementation challenges to guide a larger program and (2) to describe qualitative improvements. **Results:** The WSO BEAT pilot feasibility program achieved the prespecified primary composite outcome in 9 of 10 (90%) sites. The most common challenges were the limited access to specific medications (e.g., direct oral anticoagulants) and diagnostic (e.g., prolonged cardiac monitoring) or therapeutic (e.g., PFO closure devices) technologies. The most relevant qualitative improvement was the achievement of a more homogeneous diagnostic and therapeutic approach. **Conclusion:** The WSO BEAT pilot program suggests that developing neurocardiology collaborations is feasible. The long-term sustainability of the WSO BEAT program and its impact on quality of stroke care and clinical outcomes needs to be tested in a larger and longer duration program.

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Introduction

The interactions between the brain and the heart have fascinated researchers and clinicians from different fields for decades [1]. Furthermore, neurocardiology has recently reemerged with renewed interest as a concept involving the collaboration between cardiologists, neurologists, and other physicians treating stroke patients [2]. From a clinical perspective, most of the focus has

been placed on the diagnosis and management of highly prevalent cardioembolic causes of stroke in the young and elderly populations and on the management of timely detection and treatment of cardiovascular complications poststroke. However, there are numerous areas of uncertainty and wide practice variability between different disciplines. Thus, there is a clear need for coordinated initiatives to foster interdisciplinary collaboration.

The World Stroke Organization (WSO) Brain & Heart Task Force developed the Brain & hEart globAl initiative (BEAT), a pilot feasibility implementation program aiming at establishing clinical collaborations between cardiologists and stroke physicians. The WSO BEAT pilot project focused on atrial fibrillation (AF) and patent foramen ovale (PFO) detection and management, highly prevalent cardioembolic causes of ischemic stroke, and transient ischemic attack (TIA). The program also included the stroke-heart syndrome (SHS), given the high incidence of cardiovascular complications observed after stroke [3–5]. We herein report the results of the implementation of the WSO BEAT pilot feasibility program in 10 sites in South America, North America, Europe, and Asia.

Materials and Methods

The WSO BEAT program was conducted between August 1st, 2021, and June 30th, 2022, and was structured into five phases (shown in Fig. 1). The program followed a prespecified protocol designed by a Steering Committee and approved by the WSO Board of Directors before the project's initiation.

Objectives

The primary objective of the pilot WSO BEAT program was to assess its feasibility by achieving a composite feasibility outcome defined below. The secondary objective was to identify implementation challenges to guide a larger scale program in the future.

Definition of the Composite Feasibility Implementation Outcome

The composite feasibility outcome required the achievement of 3 quality metrics: (1) developing site-specific clinical pathways for the diagnosis and management of AF, PFO, and the SHS; (2) establishing regular neurocardiology rounds (e.g., monthly, bi-monthly, etc.); and (3) incorporating a cardiologist to the stroke team. The quantification of these metrics was performed in a survey distributed to each of the site leads at the end of the project, as outlined below.

Site-Specific Clinical Pathways

To consider this quality metric fulfilled, a specific care pathway needed to be in place for the diagnosis and management of AF, PFO, and the SHS by the end of the program.

Neurocardiology Rounds

Each site had to establish regular neurocardiology rounds attended by the stroke team and cardiologists. At least one round had to occur by the end of the program to consider this quality metric achieved.

Dedicated Cardiologist

The formal designation of a cardiologist to be actively involved in the clinical decision-making process of patients with AF, PFO, and the SHS. The cardiologist had to: (1) be available or round regularly with the stroke team and (2) attend neurocardiology rounds. The rationale behind this goal was that by having one or two cardiologists interacting regularly with the team would result in a more homogeneous and consistent approach. We intentionally did not establish any specific numeric metric for this outcome given that they were likely to vary significantly across sites.

The protocol specifically avoided using quantitative clinical outcome measures because, given the pilot and feasibility nature of the project, all analyses would have been underpowered. Additionally, we anticipated that collecting patient-label data would result in delays, challenging the feasibility of the pilot project. The protocol also considered implementing a larger scale program at a later phase to evaluate its impact on clinical outcomes.

Program Design and Implementation

Members of the Steering Committee were responsible for the design of the project and met weekly during the first three phases and on an as-needed basis thereafter.

Phase 1: Selection

During this phase, the WSO BEAT Steering Committee selected 10 sites from 8 countries. The rationale was to include a cohort of academic sites with diverse socioeconomic, cultural, and organizational profiles to test the program's feasibility in different settings with variable levels of healthcare resources. The final site selection was based on the potential interest expressed by the site lead and their likelihood of committing to the program objectives based on their previous performance in prior projects. At each site, a stroke physician and a cardiologist were designated site lead and co-lead or vice-versa. Each site was assigned a WSO Brain & Task Force member, responsible for interacting with the site leads and liaising with the WSO BEAT Steering Committee. The WSO Brain & Task Force member was responsible for organizing meetings with the site leads, ensuring the completion of each program's step within the specified deadlines, contributing to the discussion of clinical care pathways when requested by the site leads, and liaising with the Steering Committee for regular updates.

Phase 2: Development of Educational Materials

A set of educational materials and clinical decision-making tools were provided to each site. The set contained 6 recorded lectures focused on AF, PFO, the SHS, and principles of clinical decision-making (shown in Table 1). Given the known limited formal training in decision-making and risk management across the medical community [6], we included these topics in the curriculum to support the participants' understanding of how biases may influence medical diagnostic and therapeutic decisions [7] and to provide them with tools to overcome cognitive barriers to change [8]. The package also included a draft of clinical care pathways for diagnosing and managing AF, PFO, and the SHS (shown in Table 1). These pathways were developed by reviewing the American Heart Association, American Academy of Neurology, Heart & Stroke Canada, and the European Society of Cardiology recommendations

[9–14]. The aim of the clinical pathways was to serve as initial guidance for the sites to adapt them or to update preexisting ones based on their resource availability and limitations. WSO Brain & Heart Task Force members and site leads were provided with a clear timeline indicating deadlines for the completion of each phase.

Phase 3: Implementation

The total duration of the implementation phase was 5 months. Active members of the WSO Brain & Heart Task Force were assigned a maximum of two sites and were entirely responsible for completing the implementation phase by working with the local site lead. The team received regular communications from the Steering Committee about the phase goals and timelines. A kickoff meeting took place at each site after the educational materials were delivered to the WSO BEAT site leads. These meetings were held virtually between WSO Brain & Heart Task Force members, WSO BEAT site leads, and relevant site stakeholders (Fig. 1). Follow-up virtual meetings were organized at each site to monitor the site progress on the use and adaptation of the clinical care pathways, the organization of regular neurocardiology rounds, and the designation of a dedicated cardiologist for the stroke team. The contents of the talks were discussed at each site during neurocardiology rounds or ad hoc meetings. In some cases, the recorded lectures were watched individually by the site team members. These lectures were intended to provide the sites with updated concepts on the main topics covered by the program. The recorded lectures aimed to level the basic knowledge across participants in all locations.

Phase 4: Assessment

The WSO BEAT program assessment focused on achieving a composite feasibility of implementation outcome and identifying challenges. We were unable to perform on-site assessment visits because most of the program was designed at the beginning of the COVID-19 pandemic and we did not envision or budgeted any on-site visits. As such, each site lead completed an end-of-program site-evaluation survey, which was reviewed by the associated WSO Brain & Task Force member. The results of the program were assessed based on these surveys. The Steering Committee evaluated these results and developed mitigation strategies to be incorporated into a larger scale initiative.

Phase 5: Knowledge Translation

The WSO BEAT Steering Committee developed this report and planned a series of sessions at several scientific meetings, including the American Heart Association Scientific Sessions and the 10th Korea-Japan Joint Stroke Conference. In addition, the results of this feasibility program will be communicated in the WSO newsletter and presented in a webinar for the World Stroke Academy. This report will be shared with other stakeholders, including companies involved in developing and commercializing devices and drugs used to diagnose and manage brain-and-heart conditions (e.g., AF, PFO, left atrial appendage closure, direct oral anticoagulants, etc.).

Results

The pilot feasibility WSO BEAT program included 10 sites from 8 countries, including Brazil, China, Egypt, Germany, Japan, Mexico, Romania, and the USA (shown in Table 2). Of the 10 sites, two belonged exclusively to the public sector, and one was public and private.

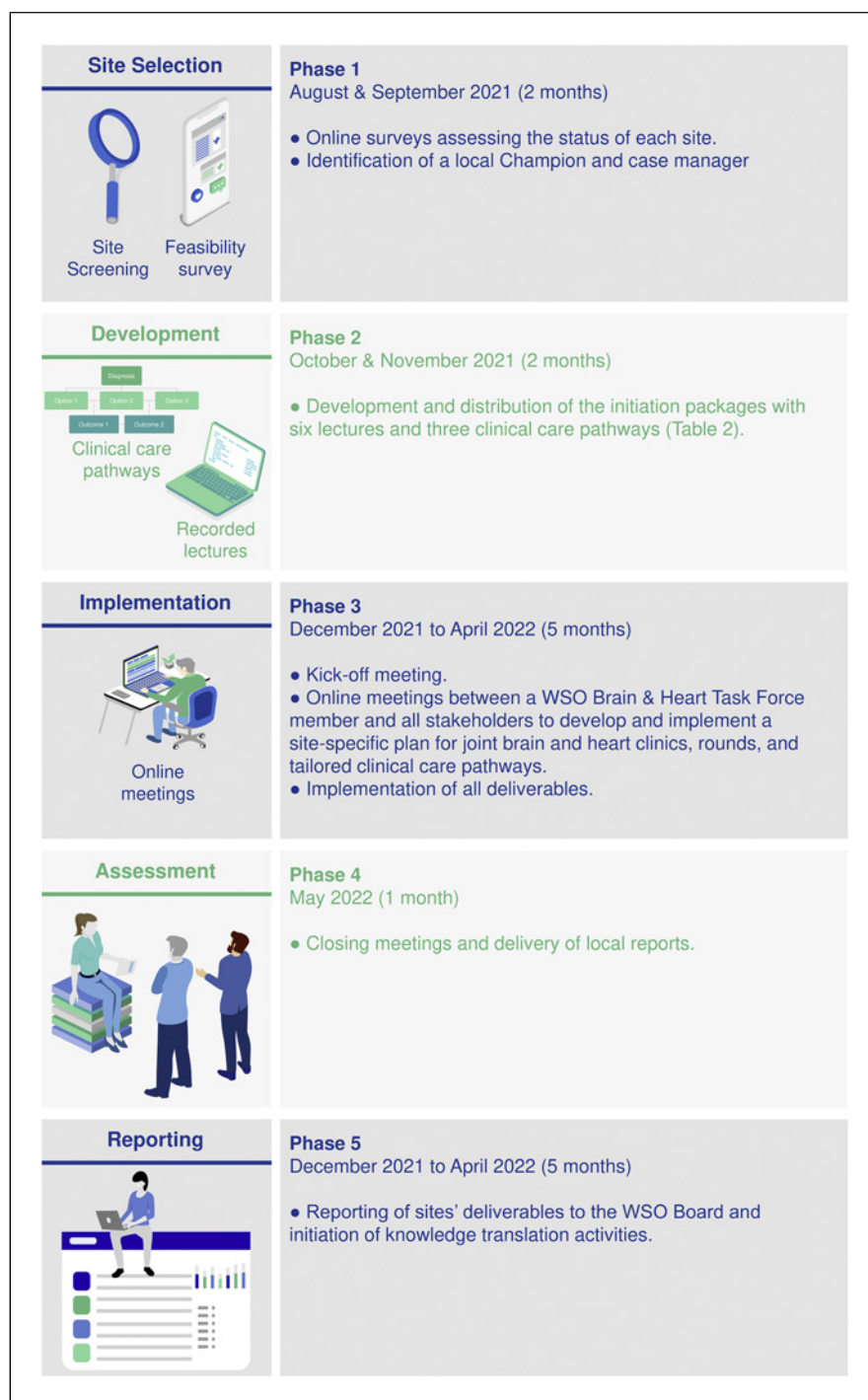


Fig. 1. Phased organization of the WSO BEAT program. Sites were selected during phase 1 based on proposed candidates by the WSO Brain & Task Force members. In phase 2, the Steering Committee worked on a roadmap and project planning, with the development of the written and video materials. The program implementation occurred during phase 3, with regular meetings between WSO Brain & Heart Task Force members, the site leads, and the local teams. Each site prepared a local report based on a prespecified questionnaire in phase 4. The Steering Committee assessed each site in phase 5 and drafted this report.

Implementation Feasibility Outcomes

Overall, the WSO BEAT program achieved the prespecified implementation goals in 9 of 10 (90%) sites (shown in Table 3). Regarding written clinical care pathways, 5 sites newly implemented them, 4 sites improved or updated preexisting versions, and 1 site did not achieve

the metric. Eight of 10 sites newly implemented neuro-cardiology rounds, one site already had regular rounds, and the remaining site failed to organize them. A dedicated cardiologist was designated in 7 sites, whereas two already had one. Only one site was not able to accomplish the latter goal.

Table 1. Contents of the WSO BEAT initiation package

Pre-recorded lectures	
topic	content
Atrial fibrillation	<ul style="list-style-type: none"> • Screening for atrial fibrillation poststroke • Use of oral anticoagulants in stroke patients with atrial fibrillation • Left atrial appendage closure in patients with stroke and atrial fibrillation
Patent foramen ovale	<ul style="list-style-type: none"> • Diagnosis and management of patent foramen ovale in stroke and TIA
Stroke-heart syndrome	<ul style="list-style-type: none"> • Diagnosis and management of cardiovascular complications poststroke
Clinical decision making	<ul style="list-style-type: none"> • Principles of clinical decision-making: lessons learned from Neuroeconomics
Clinical care pathways	
topic	content
Atrial fibrillation	<ul style="list-style-type: none"> • Atrial fibrillation diagnosis and management after stroke and TIA
Patent foramen ovale	<ul style="list-style-type: none"> • Patent foramen ovale diagnosis and management after stroke and TIA
Stroke-heart syndrome	<ul style="list-style-type: none"> • Diagnosis and management of cardiovascular complications poststroke
TIA, transient ischemic attack.	

Table 2. Characteristics of participating sites

Site #	Rounded 2020 GDP per capita	Estimated annual number of stroke/TIA patients served	Stroke unit	Funding model	Established neurocardiology team
Brazil 1	15,000	350	Yes	Private	No
Brazil 2	15,000	1,000	Yes	Public	No
China	10,000	3,600	Yes	Public	Outpatient/Inpatient
Egypt 1	3,500	1,270	Yes	Private	Outpatient/Inpatient
Egypt 2	3,500	2,190	Yes	Public	Outpatient/Inpatient
Germany	46,000	2,300	Yes	Public	Outpatient/Inpatient
Japan	42,000	1,000	Yes	Public	Outpatient/Inpatient
Mexico	8,500	600	No	Public	No
Romania	13,000	1,200	Yes	Public	No

Challenges

Some site-related challenges were identified during the implementation of the WSO BEAT program (Fig. 1, supplementary online file; for all online suppl. material, see <https://doi.org/10.1159/000530471>). Prolonged cardiac monitoring was limited at several sites because of either the lack of reimbursement or devices not being available (e.g., >72-h monitoring). We also identified a significant heterogeneity in diagnostic and screening strategies across sites. While some centers had access to implantable loop recorders, others only had access to 48-h Holters. There was a lack of reimbursement or coverage of procedures known to significantly reduce the risk of recurrent stroke, such as PFO closure. Some sites had understaffed cardiology

services or no cardiologists (e.g., Neurosciences Institute in Mexico without other specialties). We also found heterogeneous diagnostic and therapeutic approaches between inpatient and outpatient services in a German site, which was mainly driven by differences in public funding.

Qualitative Improvements

Even within a same site, diagnostic approaches were inconsistent across physicians due to the lack of clinical care pathways and because of different physician's preferences before the implementation of the program. There was general agreement amongst sites that the WSO BEAT program resulted in a more homogeneous and comprehensive diagnostic and therapeutic approach of patients

Table 3. Feasibility outcomes

Site #	Clinical care pathways	Neurocardiology rounds	Dedicated cardiologist	Challenges and opportunities for improvement	Qualitative impact
Brazil 1	<ul style="list-style-type: none"> • Preexistent, improved 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly designated 	<ul style="list-style-type: none"> • Heterogeneity in diagnostic and therapeutic approach across physicians 	<ul style="list-style-type: none"> • Reduced heterogeneity and improved consensus in the diagnostic approach • Enhanced communication between stroke physicians and cardiologists • Development of research collaborations
Brazil 2	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly designated 	<ul style="list-style-type: none"> • Availability and cost of medication and diagnostic devices (e.g., direct oral anticoagulants, PFO closure, prolonged cardiac monitoring) 	<ul style="list-style-type: none"> • Brainstorming and action plan to overcome current barriers to improved care • Improved collaborations and teamwork with cardiologists
China	<ul style="list-style-type: none"> • Preexistent, improved 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Preexistent 	<ul style="list-style-type: none"> • Need for improved education of trainees • Busy physician schedules challenging regular communication among program stakeholders 	<ul style="list-style-type: none"> • Enhanced cooperation with cardiologists • More comprehensive clinical approach
Egypt 1	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly designated 	<ul style="list-style-type: none"> • Lack of access to prolonged cardiac monitoring • Busy physician schedules challenging regular communication among program stakeholders 	<ul style="list-style-type: none"> • Increased consistency in the use of state-of-the-art diagnostic and therapeutic interventions
Egypt 2	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly designated 	<ul style="list-style-type: none"> • Lack of access to prolonged cardiac monitoring • Busy physician schedules challenging regular communication among program stakeholders 	<ul style="list-style-type: none"> • A BEAT patient registry including all stroke-heart cases was established • Increased consistency in the use of state-of-the-art diagnostic and therapeutic interventions
Germany	<ul style="list-style-type: none"> • Preexistent, improved 	<ul style="list-style-type: none"> • Newly established 	<ul style="list-style-type: none"> • Newly designated (x2) 	<ul style="list-style-type: none"> • Reduced personnel because of the COVID-19 pandemic • Lack of reimbursement for outpatient cardiac monitoring • Expansion of program for patients not admitted to the stroke unit (e.g., Neurointensive Care Units) 	<ul style="list-style-type: none"> • Improved common spirit of cooperation • Improvement of knowledge of cardiac conditions leading to stroke, cardiac complications, and interpretation of cardiac diagnostics • Standardization of investigations for the screening of the stroke-heart syndrome (e.g., troponin ordered for all patients attending the Emergency Department)
Japan	<ul style="list-style-type: none"> • Preexistent, improved 	<ul style="list-style-type: none"> • Preexistent 	<ul style="list-style-type: none"> • Preexistent 	<ul style="list-style-type: none"> • Busy physician schedules challenging regular communication among program stakeholders 	<ul style="list-style-type: none"> • The WSO program offered an alternative and enriching perspective to the way in which patients with heart and brain conditions are investigated and treated

Table 3 (continued)

Site #	Clinical care pathways	Neurocardiology rounds	Dedicated cardiologist	Challenges and opportunities for improvement	Qualitative impact
Mexico	<ul style="list-style-type: none"> Newly established 	<ul style="list-style-type: none"> Newly established 	<ul style="list-style-type: none"> Newly designated 	<ul style="list-style-type: none"> Lack of an on-site cardiology service mitigated with a collaboration with the National Institute of Cardiology 	<ul style="list-style-type: none"> Acquisition of equipment (e.g., Doppler ultrasound) New collaboration with the National Institute of Cardiology Increased number of patients referred for PFO closure A dedicated cardiologist is now reporting Holters and echocardiograms More homogeneous approach to anticoagulation and interventional procedures More homogeneous approach to anticoagulation and interventional procedures
Romania	<ul style="list-style-type: none"> Not achieved 	<ul style="list-style-type: none"> Not achieved 	<ul style="list-style-type: none"> Not achieved 	<ul style="list-style-type: none"> Busy physician schedules challenging regular communication among program stakeholders 	<ul style="list-style-type: none"> NA
USA	<ul style="list-style-type: none"> Newly established 	<ul style="list-style-type: none"> Newly established 	<ul style="list-style-type: none"> Newly designated 	<ul style="list-style-type: none"> Not being able to implement joint Neurology-Cardiology clinics 	<ul style="list-style-type: none"> Streamlining the care of stroke patients Patients with cryptogenic stroke can be very quickly evaluated Strengthening the ties between our neurology and cardiology divisions

with ischemic stroke and TIA. The site leads reported a perceived qualitative improvement in the communication and cooperation between stroke physicians and cardiologists. The program triggered action plans to overcome longstanding limitations (e.g., lack of a Cardiology Service). Additional qualitative improvements are shown in Table 3.

Discussion

To our knowledge, the WSO BEAT constitutes the first attempt to systematically develop Neurocardiology collaborations with a clinical focus. This pilot feasibility program was tested in 10 public and private academic centers from 8 countries with different cultural backgrounds, resources, and levels of academic and economic development. Despite wide variability in region and site characteristics, the WSO BEAT was successfully

implemented at 9 of 10 (90%) sites. These results are encouraging and constitute a first step toward the global development of neurocardiology collaborations.

Relevant challenges were identified at the site level. The most significant and frequent limitation faced by the participating sites was the lack of reimbursement for diagnostic technologies (e.g., prolonged cardiac monitoring) and therapeutic procedures (e.g., PFO closure). These procedures are supported by the highest level of evidence (e.g., randomized controlled trials) and by current clinical guidelines [9–19]. A joint effort should be made by international and local scientific societies in collaboration with the private sector (e.g., device companies) and policymakers to establish short- and long-term sustainable strategies to mitigate these deficiencies. We identified challenges in most of the phases, which will serve as the basis for the development of mitigation strategies for a future larger scale initiative (Fig. 1; supplementary online file).

Lessons Learned

The WSO BEAT program served to test the feasibility of implementing specific interventions aimed at enhancing neurocardiology collaborations internationally under the guidance of the WSO Brain & Heart Task Force. Several lessons were learned during the implementation of the WSO BEAT Program. First, the program was designed and budgeted during the COVID-19 pandemic. At that time, we did not plan any on-site visits and the program was therefore entirely designed based on virtual visits. In the future, the larger scale WSO BEAT program will implement a virtual setup process followed by on-site assessment visits. This will allow for a more accurate, reliable, and objective evaluation. Second, the initially estimated duration of the implementation phase (phase 3) was too short. We learned that 9 months, instead of 5, would be a more realistic timeline. Third, meetings between the WSO Brain & Task Force and site leads need to be held at least monthly to keep the momentum. Fourth, a major challenge was access to diagnostic and therapeutic technologies. This is an important source of regional inequalities. An approach to overcoming these inequalities is discussed in the next section.

Future Steps

A large-scale program including 30 to 40 sites called WSO BEAT-STROKE is currently being designed by the WSO Brain & Heart Task Force based on lessons learned from WSO BEAT. The WSO BEAT-STROKE program will test whether implementing a Neurocardiology Program can improve adherence to Level of Evidence A recommendations from clinical guidelines and will measure clinical outcomes as secondary endpoints.

This report has limitations. First, although the WSO BEAT program achieved its implementation goals, it remains unknown whether the optimized organization of stroke sites will improve adherence to best practice recommendations or clinical outcomes such as stroke recurrence, cardiovascular complications, and resource utilization. This program aimed to assess implementation feasibility. Therefore, we did not measure clinical outcomes because the analyses would have been underpowered. Future larger scale initiatives should focus on clinical endpoints. Second, considering the substantial time commitment required to conduct the program, the feasibility of a larger scale initiative is still undetermined. Third, we cannot rule out the possibility of self-reporting bias despite the outcome metrics being formally assessed by members of the Task Force [20]. Finally, since the time between the implementation and assessment was short, we cannot report on the program's sustainability at the respective participating sites.

In conclusion, the WSO BEAT pilot program showed that it was possible to initiate specific implementation measures in a group of heterogeneous sites from different countries and funding systems (e.g., private vs. public). This pilot implementation program was not intended to measure its impact on quality of care or clinical outcomes. These outcomes will need to be evaluated in a larger scale program with a different study design (e.g., cluster randomized trial). An important contribution of the WSO BEAT program is having been able to identify challenges and barriers to implementation and their respective contingency measures to facilitate a larger scale program.

Acknowledgments

WSO BEAT Steering Committee: Marc Fisher, MD; M. Cecilia Bahit, MD; Luciano A. Sposato, MD, MBA; and Gustavo Saposnik, MD, PhD, MSc. All members of the Steering Committee contributed equally to the development of this program.

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Statement of Ethics

Ethical approval and consent were not required as this study did not involve human subjects. The World Stroke Organization Executive Board approved the project (no approval number provided). Informed consent was not required because this project did not involve human participants.

Conflict of Interest Statement

L.A. Sposato: speaker/consulting honoraria from Boehringer Ingelheim, Pfizer, Bayer, Gore, and Daiichi Sankyo; research grants from Boehringer Ingelheim and Bayer; member of the Editorial Board of Neurology, Stroke, and JAHA; co-editor, neurocardiology section of Stroke. Guest Associate Editor, JAHA. S. Martins: speaker honoraria from Boehringer Ingelheim, Bayer, Pfizer, Medtronic, Penumbra, Novo Nordisk, Novartis; research grants for RESILIENT Trial from CNPq and Ministry of Health of Brazil. Research grant for RESILIENT Extend-IV, RESILIENT DIRECT TNK, PROMOTE Trial, and Hospital Moinhos de Vento/PROADI SUS from the Ministry of Health of Brazil. J.F. Scheitz: speaker honoraria from AstraZeneca. M.E. Gurol: Dr. Gurol's hospital received research grants from AVID, Pfizer, and Boston Scientific Corporation. P. Fiorilli: speaker/consulting honoraria from Medtronic and Edwards LifeSciences. C. Israel: advisory board for Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, Pfizer, speaker's honoraria for presentations and congress/travel cost reimbursement by Abbott, Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, and Sanofi. K. Kusano: speaker Honoraria from Daiichi Sankyo Ltd., Nippon Boehringer Ingelheim, Biotronik Japan, Bayer Yakuhin, Pfizer, and Medtronic Japan, and research grants from Medtronic Japan, Hitachi, Biotronik Japan, Mebix, and JSR. O. Manssour: speaker/consulting honoraria from Boehringer Ingelheim, Neurovasc, and Stryker Guest Associate Editor, Frontiers in neurology. Developer of ESN-platform for stroke services clustering (Patent: No. ETM193883). S.R. Messé: research grants from WL Gore,

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Author Contributions

L.A. Sposato: acquisition, analysis, or interpretation of data, drafting of the manuscript, agreement to be accountable for all aspects of the work, and final approval of the version to be published. S. Martins, A. Arauz, and J.F. Scheitz: interpretation of data, critical revision for important intellectual content, and final approval of the version to be published.

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Data Availability Statement

All the data used for the manuscript are shown in the manuscript and online supplementary file. Further inquiries can be directed to the corresponding author.

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