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Journal

eNeurologicalSci, 1(2)

ISSN

2405-6502

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et al.

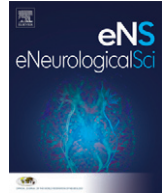
Publication Date

2015-06-01

DOI

10.1016/j.ensci.2015.09.003

Peer reviewed



Cost and cost-effectiveness analysis of a bundled intervention to enhance outcomes after stroke in Nigeria: Rationale and design



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ARTICLE INFO

Article history:

Received 28 May 2015

Received in revised form 7 September 2015

Accepted 13 September 2015

Available online 28 September 2015

Keywords:

Cost-effectiveness

Costs and cost analysis

Stroke

Nigeria

ABSTRACT

The economic and social costs of stroke to the society can be enormous. These costs can cause serious economic damage to both the individual and the nation. It is thus important to conduct a cost effectiveness analysis to indicate whether an intervention provides high value where its health benefits justify its costs. This study will provide evidence based on the costs of stroke with a view of improving intervention and treatments of stroke survivors in Nigeria.

This study utilizes two types of economic evaluation methods – cost-effectiveness analysis and cost–benefit analysis – to determine the economic impact of Tailored Hospital-based Risk Reduction to Impede Vascular Events after Stroke (THRIVES) intervention. The study is conducted in four Nigerian hospitals where 400 patients are recruited to participate in the study. The cost-effectiveness of THRIVES post-discharge intervention is compared with the control Intervention scenario, which is the usual and customary care delivered at each health facility in terms of cost per quality adjusted life years (QALYs). It is expected that successful implementation of the project would serve as a model of cost-effective quality stroke care for implementation.

Award Number: U01 NS079179.

Trial registration: RL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01900756

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1. Introduction

Stroke is a disease with enormous health and economic implications. In 2005, the World Health Organization reported that 6 million persons died from stroke each year or 11 persons every minute [1]. In African countries where incomes are low, these enormous costs can cause serious economic damage to both the individual and the nation. These economic impacts of stroke with stroke-related costs can be as high as 3% to 4% of the annual health-care budget in some countries [2]. A review of the costs of stroke in low and middle-income countries was conducted and found that the highest mean direct medical cost of stroke was US\$ 8424 in Nigeria while the lowest mean cost of stroke was in Senegal (US\$ 416) [3]. These costs are mainly predicted by the length of stay and stroke severity.

The best intervention process of managing stroke survivors is still fraught with controversies especially as they concern the economic impacts of such interventions. This is because of its demand on scarce health resources of either the patient, family, or the health system in general. This therefore calls for defining the relative value of different stroke interventions with a view of identifying the most cost effective. Despite this, many of the past studies have failed to provide information about which treatments are the most efficient in reducing overall disease burden in the setting of economic constraints [4,5].

Incidentally, little is still known about the economic implications of stroke in many developing countries including Nigeria. Many stroke evaluation and treatment policies may result in benefits to health that is considered worth their cost [6]. Despite the studies on stroke in Nigeria, there are very few of the previous studies that have investigated the economic costs of stroke as well as compared the cost effectiveness of stroke intervention program in Nigeria. It is therefore important to contribute to this discourse by simultaneously assessing the health effects

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and costs of different health interventions; cost-effectiveness analysis provides a research methodology to make such comparisons.

Nigeria is currently experiencing a rapid epidemiological transition, where the predominant cause of mortality is shifting from the infectious diseases and perinatal conditions to chronic diseases and injuries. Stroke has recently become one of the main health conditions accounting for disability and mortality in the country. It has been shown that high and increasing rates of stroke affect people at much younger ages in SSA than in developed countries [7]. Post stroke survival rate is anticipated to increase in developing countries due to better treatment and management; hence it generates the necessity for arranging rehabilitation for stroke survivors in the most effective way so as to give them the best possible quality of life [8,9,10].

Earlier studies on stroke in Nigeria have focused on the issues of determinants of health-related quality of life (HRQoL) among stroke survivors [11,12] as well as the prevalence of strokes. Some studies have also investigated costs of stroke using different economic evaluation approaches [13,14] and Care environments for stroke rehabilitation as well as some others on the factors that predict those changes on their physical, mental, and social health during the recovery phase [15,16,17]. A key issue from most of the studies is the need to generate evidence to support development of effective health policy and strategy related to services for the stroke survivors. The issue of cost effectiveness of different options becomes more crucial given the resource constraints that many government health sectors face as well as the high poverty incidence and the lack of health insurance to mitigate the health shocks arising from the stroke condition [18].

However, in the past decade, there have been extraordinary medical advances in the treatments. While many may not survive stroke events, there is a growing proportion of persons surviving the event although they still require clinical management. Although many people survive stroke because of modern technology, most of them still live with impairment, disability, or handicap. Rehabilitation reduces disability and maximizes functional ability for stroke survivors with disabilities. Research has indicated that multidisciplinary, early, and intensive rehabilitation significantly reduces disability [19,20,21]. Rehabilitation can restore function and prevent permanent disability in patients with stroke [1]. It is important to conduct a cost effectiveness analysis to indicate whether an intervention provides high value depending on assessing whether its health benefits justify its costs [22]. Where interventions have little values for its cost it might not be worthwhile for full implementation. The ultimate goal of any stroke interventions is to improve the health-related quality of life (HRQoL) of survivors ensuring that they are enabled to fulfill their roles and purpose in life after the event [23]. Unfortunately, there has been scarcity of research to assess the cost-effectiveness of different interventions for post-stroke cases despite the increasing importance of this service to minimize post-stroke functional problems [5,24].

The Nigerian health system is faced with multiple constraints from both infectious and non-communicable diseases (NCDs), hence, there is a need for more evidence on the cost-effectiveness of the rehabilitative care model to recommend a better alternative course of treatment to stroke survivors. This has the possibility of benefiting not just the patients but also the Nigerian health system thereby ensuring that rehabilitation services offer good value for money, so that health care providers are encouraged to provide such services to facilitate access to care and quality of care. This study will provide evidence base on the costs of stroke with a view of improving intervention and treatments of stroke survivors alongside efforts to bring infectious diseases under control in Nigeria. This paper therefore presents the designs and methods of a study aimed at examining the economic impact of stroke in Nigeria.

2. The THRIVES project

The Tailored Hospital-based Risk Reduction to Impede Vascular Events after Stroke (THRIVES) project is designed to improve the

delivery of secondary stroke preventive services in Nigeria by designing and testing a chronic care model-based intervention. This study proposes to examine the impact of a tailored intervention on reducing blood pressure in a cohort of stroke survivors. It is expected that the successful implementation of the project would serve as a model of cost-effective quality stroke preventive care for implementation in other countries in Sub Saharan Africa [26].

The overall objective of the cost component of the THRIVES project is to fully capture the economic impact of care after stroke. The study shall focus on intervention and control groups. The control group shall follow standardized version of the usual and customary care delivered at each hospital selected for the study while for the intervention group, we shall utilize a process that follows 5 stages as follows:

1. *Pre-appointment phone text*: The day prior to each visit, the patients will receive a pre-appointment reminder telephone text sent by the clinic staff asking patients to arrive an hour early for their appointment.
2. *In-clinic educational video*: While in the waiting room the patients will be asked to watch a stroke awareness educational video. The video had been developed by the Nigerian Stroke Society in conjunction with the study Task Force containing dramatized stroke scenarios, educational messages, and questions on the material taught with delayed responses. The video will run for repeatedly every 30–45 min throughout the clinic.
3. *Patient report card*: When the patient meets with the physician, the material of the video will be briefly discussed. The physician will show the patient the customized report card and go over the patient's current vs. optimal control of key stroke risk factors.
4. *Post-clinic phone text*: At the end of given THRIVES clinic, the physician who saw the patient will send a brief structured telephone text to the patient's mobile (cell) phone emphasizing the areas requiring better risk factor control. Caregivers or family members are encouraged to participate in all aspects of the care intervention because they may be most responsible for medication adherence and improving lifestyle habits. The intervention will last one year after stroke onset.
5. *Outpatient stroke registry*: Each patient will be tracked in an electronic registry. The registry will contain data written on the report cards. It also will contain contact information on how the subject can be notified for care coordination telephone texts.

As part of efforts to ensure quality of intervention, the report card and phone texts will only be issued to, and discussed with intervention patients. As part of efforts to make the process culturally relevant, the interventions are also designed in Yoruba language in a bid to cater for the less English literate patients. The messages are carefully designed and validated by telecommunication experts who are part of the study's multidisciplinary task force committee to target adherence to risk factor. This messages are delivered to intervention patients at the various time points of the study. Follow-up phone calls are put through to patients to ensure that they are recipient of such messages. The control (usual care) patients are not scheduled to come to the clinic on the same day as intervention patients, and control patients will be scheduled to see other non-investigator neurologists by the research coordinator.

In a bid to address intervention fidelity, the study developed defined manuals/protocols/algorithms that explicitly spell out the THRIVES study purpose, goals/objectives, and essential or critical elements and all the content that must be covered. In addition, THRIVES manuals contain detailed information about each proposed encounter, including how much time should be allotted to cover each bit of content, what behaviors are to be demonstrated or role-played, and what strategies are used to check participants' understanding during the encounter. Each of these elements is then monitored to insure fidelity. Furthermore, to minimize variance in intervention delivery and enhance a high degree of structure in the intervention design, all physicians are properly

(and repeatedly) trained in THRIVES study procedures. A THRIVES task force comprising the investigators, physician, statisticians, pharmacists, nurses, dieticians, physical therapists, administrators, religious, government representatives of the Nigerian Stroke Society and telecommunication experts, who were part of the initiation and intervention validation sessions, evaluate the process using checklists and structured instruments; review the progress of the trial at regular intervals and make recommendations about any local adaptations to facilitate implementation at each site, and assesses the extent of implementation.

3. Methods

The cost effectiveness of the THRIVES project shall be done on the assumption that the intervention decisions are made in the interest of society as a whole. Hence the approach shall be to conduct the study from a societal perspective. The study is driven by a main hypothesis that *in a study sample of stroke patients the THRIVES intervention will be a dominant (reduces health system costs), highly cost-effective or substantially cost-effective treatment.*

3.1. Design

The THRIVES study aims at estimating the costs, cost of stroke disease and cost-effectiveness of the THRIVES post-discharge intervention, compared with usual and customary care. This is done using two types of economic evaluation to determine the economic impact of THRIVES intervention. These include the cost-effectiveness analysis, where the incremental costs associated with an incremental change in a health outcome are determined, and the cost-benefit analysis, where the incremental costs are subtracted from incremental monetary benefits. Both methods can effectively indicate the net benefit of health intervention. However, cost-benefit analysis differs from cost-effectiveness analysis in that health outcomes are also expressed in monetary forms rather than in units of health. This method is very useful since when both the costs and the benefits of an intervention are expressed in monetary forms, it becomes clearer to determine whether the benefits outweigh the costs [25].

3.2. Setting and participants

In order to capture many patients with varied background, THRIVES study will be carried out in Oyo and Ogun states located in the South-western part of the Nigeria. Oyo state has a population of 5.592 million while Ogun state has a population of 3.728 million. This study is conducted in four hospitals in Nigeria. The hospitals are University College Hospital, Ibadan, Blossom Centre for Neuro-rehabilitation, Federal Medical Centre, Abeokuta and Sacred Heart Hospital, Abeokuta. Two of the hospitals are government owned while the other two are non-governmental. The diverse nature of the hospital makes it easy to capture patients from varied background. The University College Hospital Ibadan is the first teaching hospital and for a long time the only teaching hospital in Nigeria. It has 850 bed spaces and 163 examination couches. The second government owned hospital is the Federal Medical Center, Abeokuta, a 250-bed regional tertiary center that receives patients from Ogun and neighboring states and countries. The hospital relates closely with community care clinics within and outside the Abeokuta metropolis and in addition receives referral from all over Nigeria and SSA. The non-government owned hospitals are the Blossom Center for NeuroRehabilitation, Ibadan, and Sacred Heart Hospital, Abeokuta. Blossom Center for NeuroRehabilitation was established in 2010 through the support of the World Federation for NeuroRehabilitation as the first center for NeuroRehabilitation in East, West and Central Africa while the Sacred Heart Hospital, Abeokuta, which was established in 1895 as the first Catholic missionary secondary medical care center in Nigeria. It has built considerable goodwill and quality in its service delivery all through the years [26]. Since stroke patients are recruited

from outpatient services of the four medical facilities, these four hospitals therefore capture key aspects of the diverse South Western Nigeria population as well as hospital types. To minimize any form of bias in subject recruitment, a statistically generated subject randomization, triple-blinded in design template is being used to enroll potential subjects who qualify after being screened with the study's criteria.

From these hospitals, 400 patients will be recruited to participate in the study. These participants will then be randomly allocated to those that will benefit from THRIVES intervention and those that will benefit from the standard post discharge management. The allocation will be done in ratio 1:1. We will however exclude the incidence of recurrent stroke in the duration of the follow-up. This is due to the fact that although Stroke, being a recurrent vascular event is one of the alternative outcome measures to Systolic Blood Pressure (SBP), its incidence is excluded since our sample size is not large enough to detect differences in recurrent vascular risk during 12-month duration of follow-up.

Being an interventional RCT study, we shall follow a procedure that is triple-blinded in design – Patients, Investigators, Biostatisticians and Research Coordinators. The patients prior to enrolment into the study do not know which of the intervention arms they are randomized into. The principal research coordinator centrally performs the randomization. This is done using a statistically generated randomization template and disseminated to site research coordinators who implement it. In addition, other physicians (senior registrars and registrars) will be employed to see both intervention and control patients thereby limiting the investigators any form of contact with the patients. Trained research coordinators (blinded assessors) who are blinded to the randomization arm (and with no contact with THRIVES clinical team) will also be engaged to collect study outcomes on all enrollees across study sites.

In all cases, written informed consent shall be obtained from the participants. This informed consent form will be translated into local language and administered to the patients. Ethical approval has been obtained from the institutional review boards of the Medical University of South Carolina, the University of California at San Diego, the University of Ibadan/University College Hospital, Federal Medical Centre Abeokuta and the Sacred Heart medical Centre.

3.3. Timeline

The proposed time for the intervention is 12 months. The baseline measurement period is regarded as Time zero (T0). Post treatment assessments shall also take place one month after baseline (T1). There will also be three follow-up assessments in here months, six months and 9 months after the baseline (called T2, T3, and T4 respectively).

3.4. Interventions

THRIVES has been structured to systematically combine three management procedures. These are the CCM, component of delivery system, the self-management support and the clinical information system. The CCM component of delivery system is redesigned by introducing increased follow-up visits, pre-appointment phone texts while the self-management support is designed to include patient report card, post-clinic follow-up texts and waiting room educational video. The clinical information systems on its own are designed to include patient record card as part of medical chart, and hospital registry. The intervention is in five parts over the period of one year. This has been stated earlier and the details are in another publication [27].

3.5. Outcome measures

The outcome measures shall be expressed in terms of quality adjusted life years (QALYs). The calculation of QALY makes use of both quantity and quality variables. The quality variable is the utility, which is represented by the value which stroke patients attach to their current

health status while the quantity variable is represented by the life years gained. The utility shall be derived from the health-related quality of life in stroke patients (HRQOLISP). Based on this, cost-effectiveness of the therapies was estimated in terms of cost per unit of function gained and cost per QALY gained.

4. Statistical analysis

The economic impact analysis assesses the cost–benefit and the social welfare of the THRIVES intervention. This study uses two methods – cost effectiveness analysis and the cost benefit analysis – to measure the economic impact of THRIVES in Nigeria.

4.1. Cost effectiveness analysis

The methodology utilized is the cost-effectiveness analysis, which compares the health benefits and costs of the intervention care and the usual care for stroke survivors. The cost-effectiveness ratio is expressed in terms of naira per health outcome. This is compared for both intervention and the control group. This study investigates which option is economically better in terms of dominance. If an option is both better and less expensive than an alternative, we say that the intervention *dominates* the alternative.

Effectiveness is defined as an improvement in functional status and quality of life. Baseline characteristics such as sex, stroke pathology, cognitive problems, functional score, patient's age, and length of stay will be presented with descriptive statistics, and the differences between two groups being assessed. The analysis involves computing the *incremental cost-effectiveness ratio* (ICER), which measures efficiency and estimates the additional expenditures required to gain additional health benefits when a more effective and expensive strategy is undertaken. The ICER is calculated for both the cost utility analysis (CUA) and the cost effectiveness analysis (CEA) using the following formula

$$\text{ICER} = \frac{C_i - C_c}{E_i - E_c}$$

where

C_i	Annual total cost of the intervention group.
C_c	Annual total cost of the control group.
E_i	Effects at the 6 months follow-up for the intervention group
E_c	Effects at the 6 months follow-up for the control group.

ICER is expressed as the incremental costs per point improvement on the primary outcome measure (QALY). This is then obtained when the difference in the (incremental) costs of the intervention and that of the usual care is compared with the difference in the outcomes (incremental effects) by dividing that of the cost with that of the outcomes. It should be noted that some studies have also used *average* cost-effectiveness ratio, which is the cost of an intervention divided by the benefit. However, the average cost-effectiveness ratio is not utilized here because of its limited usefulness and ability to provide misleading estimates, when compared with the incremental cost-effectiveness ratio.

There are always uncertainties surrounding the estimation of ICER [28]. In order to assess that the results from the ICER are robust and plausible, we conducted a bootstrap simulation. This indicates the uncertainties surrounding ICER by estimating a 95% confidence interval. The subsequent bootstrapped cost effective ratios will then be plotted in graph with difference in cost along vertical line and differences in effectiveness in the horizontal line. The import of the graph of the bootstrapped ICER is that it depicts the cost effectiveness acceptability curve by showing the maximum amount of money that a society is prepared to pay for a gain in effectiveness. This amount is regarded as the ceiling ratio. We shall compute the mean cost differences between intervention and control group. The mean costs so calculated are direct

health care costs, direct non-health care costs, indirect non-health care costs, and total costs. Outcomes with a P value of <0.05 were considered statistically significant. The 95% confidence intervals of the cost differences shall also be estimated with approximate bootstrap confidence (ABC) intervals. After calculating the ICER, we shall also conduct a sensitivity analysis.

4.2. Cost–benefit analysis

The cost–benefit analysis (CBA) puts the monetary value on both cost and benefits derivable from THRIVES. To calculate the overall impact of THRIVES; we value both costs and benefits for each patient separately in monetary terms, sum the net impacts and compare them, assessing whether it is desirable through the use of decision criteria (e.g. if the benefit cost ratio defined as benefits divided by costs is greater than one, THRIVES is worthwhile). Discounting technique is applied for estimating cost benefit analysis by adjusting for the time value of money since the benefit of THRIVES will accrue over time. We examine the distribution of costs to determine whether the data needs to be transformed and whether two-part modeling is required to account for subjects with zero expenditure. If there is zero-inflation we will use marginalized two-part models [29] or two-component mixture models [30]. Comparisons are made with and without adjusting for baseline imbalances of patient characteristics. The series of analyses include a) comparing the direct costs of THRIVES plus the associated costs for utilization among subjects in the intervention arm vs. associated costs of utilization among subjects in the usual care arm during the one-year period subjects were enrolled in the RCT after randomization; b) redoing the analysis but extending the time period from time of randomization to the most recent time with available data; and c) repeating the aforementioned two analyses but including the future costs based on predicted risk of vascular events.

Perhaps, difficulty might arise in monetary measurement of the benefit of THRIVES in spite the clear definition and desirability of its outcome [31]. In this case, we shall utilize shadow pricing and costing methodology to estimate the associated costs. Since health status is a dynamic concept, while the above approaches focus on a measure of health status at a particular time, another approach that attempts to include the duration as well as the quality of health output is the Quality Adjusted Life Year (QALY), where the number of years of life gained from an intervention is adjusted by a measure of their quality assuming a possibility of comparisons and trade-offs between the quality and the quantity of life. A year of perfect health is scaled to be 'worth' 1 and a year of less than perfect health 'worth' less than 1. Death is commonly indicated by 0, though in some situations there may be states regarded as worse than death and which would have negative numbers attached to them. This is particularly relevant to the evaluation of THRIVES given that it enables survival for a certain period of time at a less than perfect state of health. This study will therefore measure the present value of future years of lifetime lost through premature mortality plus the present value of the adjustment to years of future lifetime to allow for the average severity (frequency and intensity) of any mental or physical disability caused by stroke. The cost-effectiveness of THRIVES post-discharge intervention will therefore be compared with the control Intervention scenario which is the usual and customary care delivered at each health facility and this shall be assessed in terms of cost per LY saved and cost per QALY saved.

During the baseline, the responses shall be compared for both the intervention and the control groups. Arithmetic mean shall then be used to describe the cost for the different groups. We will check the structure of the data. Where the cost data are skewed, we will test for median/quartile differences in the costs between the two groups using the non-parametric methods or quartile regression [32]. When the distribution of the data conforms to the normal distribution, the statistical difference in cost shall be compared using the t test.

Since the study will last for more than one year, the costs shall be calculated in real values corresponding to the base year prices. We shall calculate the mean cost per patient for both THRIVES and usual therapy and thereafter calculate the mean cost difference between these regimens over the duration of the study, by type of cost and allocation in both trial and usual care settings. We shall compare basic characteristics and costs of healthcare for the intervention and control groups. We will use the chi square (χ^2) test for categorical variables and the 2-sample t test for continuous variables, depending on their distributions. We will use non-parametric and quantile regression methods to compare the mean monthly costs of healthcare and caregiving services for intervention and control groups' patients who will survive the entire 48-month study period with follow-up data available at 12 months, 24 months, 36 months, 48 months or all.

4.3. Sensitivity analysis

We shall explore three different scenarios for sensitivity analysis.

- i. First we shall assume that the loss of productivity as measured by indirect cost is just 80% as against 100% loss in the base case. This is consistent with some earlier studies that a 100% loss of work time corresponds to an 80% reduction in productivity [33]
- ii. Secondly, we shall also explore a scenario where all costs for physicians were replaced by costs for nurses. This is on the assumption that in most of the cases for a post stroke survivor, the intervention performed by a nurse could be effective as the one performed by a—more expensive—physician;
- iii. The third scenario is to use different measures for indirect cost. We will use the self-reported income from the questionnaire and compare to the national minimum wage schedule of the country. We will determine the status of the respondents on the Government salary scale and compare with the self-reported value.

4.4. Procedure for analysis and valuation of costs and benefits

Following from the two methodologies that will be used in computing the economic impact of THRIVES, the following steps shall be followed in for the analysis.

- a) Obtain the direct cost of all expenses on the intervention and usual care.
- b) Obtain the indirect cost on loss of productivity as a result of morbidity and mortality both to the patients and the major caregivers.
- c) Obtain other illness-specific costs such as (special education and residential-care costs) for all patients stricken with the diseases.
- d) Obtain the measured benefits in terms of life years (LYs) saved, quality-adjusted life years (QALYs) saved, and lifetime medical costs saved.
- e) Obtain the monetary benefits of the intervention
- f) Conduct both the cost effectiveness (including incremental cost effectiveness ratio) and the cost benefit analyses

The starting point will be to consider the adequacy and completeness of the returned questionnaires. It is usual for respondents to be wary of answering cost and income questions. We therefore anticipate some missing items. Since the data will be collected over 5 periods, some of the missing measurements shall be handled using multiple imputations [34].

We will use a generalized linear mixed model (GLMM) approach to fit the association models assessing the association between treatment and cost outcomes adjusting for covariates collected at baseline. The general model will have the following regression format: $E(Y_{ij}|X_{ij}, Z_i) = g^{-1}(X_{ij}\beta + Z_i + \epsilon_{ij})$, where g is a monotone link function and Y_{ij} is a vector of the responses for the i th subject at time j and X_{ij} and Z_i represent

vectors of fixed and random effect covariates, respectively. We will consider link functions depending on the scale of the outcome. For example, we will use an identity links to fit models for outcomes measured in a continuous scale and log link for count outcomes.

We will compare models using model fit statistics such as the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). All models will be assessed for goodness-of-fit using residual analysis and influence statistics [35]. When diagnostics via residual analysis shows that the continuous outcomes do not conform to the assumption of normality, we will use Gamma distribution with a log-link to model the cost outcomes. When there is inflation of zero values, we will also consider marginalized two-part models or mixture models [36] that are suitable for modeling zero-inflation. All statistical tests will use a two-tailed $\alpha = 0.05$ level of significance and will be performed using SAS, STATA or SPSS software depending on availability.

4.5. Study tools and valuation of the costs

The valuation of the different types of cost shall be calculated using the available information. There are two main types of costs that are associated with stroke and they are direct and indirect costs. Direct cost or the immediate cost resulting from treatment included medical therapy, physician visits, and in-patient stay. The indirect costs were inability to work (during physician visits or hospitalization) incurred by patient.

This study will examine the following cost categories

- a) Intervention costs,
- b) Direct healthcare costs, and
- c) Indirect and spiritual Costs

4.5.1. Intervention costs,

The intervention costs include all the costs that contributes to the development and administration of THRIVES Intervention. The THRIVES intervention costs will be measured as the actual use of resources and the data will be obtained from THRIVES and hospital records. These resources will be based on the registered time of the professional spent on the treatment. These costs shall be measured using the logbooks of professional while the other costs shall be obtained from the cost questionnaire for the patients at the measurement points in the study (T0–T3). Table 1 presents the different tools for data collection.

We shall distinguish between start-up costs of initiating THRIVES versus the maintenance costs of conducting the program. Start-up costs include the time for the PIs to train THRIVES staff and the training time required by the staff to become proficient in carrying out their duties. Time components will be valued at appropriate salary levels. Additional start-up costs include a computer to store a registry for tracking contact information and control of risk factors. Maintenance costs of THRIVES include clinic room charges, printing of materials, and phone text costs for care coordination. We will not record the time spent by the blinded RA to evaluate the intervention, as this activity is not part of usual care. We will query the administrative databases of all hospitals to count the total number of hospitalizations (bed-days), ED visits, outpatient visits to primary care, outpatient visits to subspecialists related to stroke prevention, prescriptions medications related to stroke prevention, and laboratory tests related to stroke prevention. We will obtain the cost equivalents of each of these services from the Oyo State and Ogun State governments. We will also predict future costs by modeling the number of future vascular events based on the net difference in SBP levels found in the two arms of the study and obtaining the average cost per vascular event in the South West Nigeria. In estimating the cost of self-monitoring intervention, the cost of nurse's time for 30 min tutorial on BP measurement was estimated. Salary of the nurse would be obtained from average salary of a nursing sister in the federal government employment in Nigeria (we have chosen salary grade 12 step 1).

Table 1
Data requirement and collection tools.

	Source of data
<i>Direct healthcare costs</i>	
Drugs	Hospital records combined with patient questionnaire responses
Imaging and Diagnosis	Hospital records combined with patient questionnaire responses
Laboratory examinations	Hospital records combined with patient questionnaire responses
Consumables	Hospital records combined with patient questionnaire responses
Medical procedures	Hospital records combined with patient questionnaire responses
Clinical Consultation visits	Hospital records combined with patient questionnaire responses
Inpatient rehabilitation	Hospital records combined with patient questionnaire responses
Cost professionals	Hospital records
a) Physicians	
b) Nurses	
c) Physiotherapists	
d) Others	
Cost of Hospitalization	Hospital records
Cost of Rehabilitation	Hospital records combined with patient questionnaire responses
<i>Direct non-healthcare costs</i>	
Transportation (Number of visits to facilities (per week))	Patient/Carer Questionnaire
Social care	Patient/Carer Questionnaire
<i>Productivity costs</i>	
Cost of productivity lost by the patient	Patient/Carer Questionnaire
Cost of informal care by family, friends and voluntary organizations (not paid for)	Patient/Carer Questionnaire
Cost of paid care (number of hours)	Patient/Carer Questionnaire
<i>THRIVES intervention costs</i>	
Costs for training	THRIVES data collection journal
Cost of printing manuals	THRIVES data collection journal
Cost of medical personnel involved in the intervention (using the number of hours involved)	THRIVES data collection journal
Phone texts (pre-appointment and post clinic)	THRIVES data collection journal
Production of Video and media costs	THRIVES data collection journal
Patient report card	THRIVES data collection journal
Outpatient stroke registry	THRIVES data collection journal
Time usage for health care personnel	THRIVES data collection journal
Training of personnel	THRIVES data collection journal
Administration,	THRIVES data collection journal
Other costs	THRIVES data collection journal

The cost of printing including the BP chart and other documents for medical records will be obtained from the University of Ibadan printing press while the cost of the BP apparatus shall be obtained from the manufacturer. Since the BP apparatus is an asset with a life span of more than a year, we have amortized the apparatus for a period of 5 years. Although the intervention happens in one year it is expected that the benefit will cover more than one year. We expect this benefit to be for about 10 years; hence the total investment on the intervention is amortized over 10 years. Nigeria has a high inflation rate, hence where the cost of an item is more than a year we also account for the effects of inflation. As a result, the costs will be deflated by the 7%, which is the average inflation rate between 2010 and 2013. We shall also include the costs of training of the medical personnel involved in the intervention. Such costs include the costs of training a nurse or a pharmacist or a nurse for the intervention was estimated. The training cost was estimated to require about 10 h of a medical consultant's time.

The cost of medical consultants' time and other personnel time will be estimated using the average salary of medical consultants and other personnel in Nigeria. In addition, we shall include the costs of the offices

used as well as the staff on the intervention project. Finally, the communication costs of the text messages shall be calculated using the National Communication Commission (NCC) approved costs of text messages in Nigeria.

Quantities of items used in cost estimation were derived from case notes of patients, interview with health personnel and patients, and hospital records. Each cost estimate obtained for an episode will then be converted to an annual or quarterly estimate as the case may be. The difference between the cost of intervention and cost implication of the control group is expected to be the true cost of the intervention.

4.5.2. Direct health care costs

Direct healthcare costs include diagnosis, medication, inpatient care and outpatient care. They are costs related to the patient. The cost of drugs shall also be computed. In this case, we shall identify the actual drugs taken as well as the relevant dosage and frequency of use that will be applied. The relevant unit cost shall be determined from the market prices before being used to arrive at the total drug cost per patient for these drugs. Where this is impossible we shall rely on the judgment of the respondents as given by questionnaire responses. The cost of transport shall be calculated as the mean distance per destination multiplied by the cost per kilometer.

For patients who had to be on admission as a result of the stroke, the cost of the stay would be calculated using the average length of stay for stroke as documented in the hospital records. This is subsequently multiplied by the daily cost of hospital stay. The cost of providing health care to stroke survivors patients was estimated in the baseline so as to assist in determining the extra cost which the interventions to improve management of stroke survivors will consume.

4.5.3. Indirect costs

In addition, we shall estimate indirect costs associated with the disease. Indirect costs are measured as the opportunity costs (loss productivity) of loss of income of patients and relatives for the whole illness episode. We consider both the income loss of the patient as well as the income loss of the carer if the carer is not a professional carer. The mean hourly wage rate shall then be used to cost direct informal care. In situations where the actual occupational status of the informal carer cannot be ascertained, we shall proxy the income loss to be equal to the current minimum wage rate of \$119 (18,000 Nigerian Naira) per month in Nigeria. In addition we shall include spiritual costs because of the potential of the spiritual sphere to reduce the biographical impact of stroke [37]. Income loss of the patients (and informal carer) shall be accounted for in the indirect cost calculations. These data shall be collected from the field survey both at baseline and after intervention stages.

4.6. Valuation of benefits

Health benefit is measured in many ways, including conditions diagnosed or prevented or life-years or quality-adjusted life-years (QALYs) gained.

4.6.1. Non-financial benefits

Health benefit in this study is measured as the life-years or quality-adjusted life-years (QALYs) gained which reflect the benefits from longer life or better quality of life. In this study, we assume that the QALY is a useful benefit indicator as it assesses how long a person lives and how persons assess quality of their lives during their lifetime.

4.6.2. Financial benefits

It is possible to monetarily quantify the benefits associated with health intervention, which could be direct or indirect [38]. The direct economic benefits of health interventions consist partly of costs averted due to the faster recovery from the stroke. This includes the treatment costs saved due to more recovery from stroke and the days gained

from less illness. The patient or policymaker is asked about how much he or she is willing to pay for health benefits.

The indirect economic benefits related to health improvement refer to the benefit arising from productivity effect of improved health [39]. These are traditionally split into two main types: gains related to lower morbidity and gains related to fewer deaths. In terms of the valuation of changes in time use for cost–benefit analysis, the convention is to value the time, which would be, spent ill at some rate that reflects the opportunity cost of time. It is argued that whatever is actually done with the time, whether spent in leisure, household production, or income-earning activities, the true opportunity cost of time is the monetary amount, which the person would earn if they were working.

5. Current study status and conclusion

The THRIVES project has now entered the RCT phase. Recruitment of potential subjects has begun in earnest from the study sites. From subject's database that has been in construction since the onset of the project, subjects are being consented and enrolled. Prior to the commencement of the RCT phase of THRIVES study, specific strategies ranging from provision of Technical Advice, Advocacy and Capacity building were incorporated in a bid to ensure smooth implementation process. With respect to provision of technical advice, consecutive, intensive and rigorous intervention validations sessions were conducted and championed by a multidisciplinary committee (Task Force Committee) comprising physician investigators, statisticians, pharmacists, educators, social workers, nurses, telecommunication experts, dieticians, physical therapists, administrators, and religious, community representatives, government and Nigerian Stroke Society. Constituted to review and make recommendations to the RCT phase of THRIVES study, THRIVES intervention (Patient Report Card, mobile text messaging and in-clinic educational video) underwent refinement and validation. As a result, the interventions evolved to a readable patient report card with targets reflecting evidence based stroke risk factor control recommendations, clarification of personnel responsible for specific tasks; identification of cost effective structures appropriate for delivery of messages, and for the video, the development of dynamic educational tool consistent with the African culture and lifestyle.

From an advocacy point of view, familiarization visit was paid earlier this year to key stakeholders at the University College Hospital, Ibadan, Nigeria by the Principal Investigator of THRIVES study. Furthermore, capacity building sessions were conducted for specific subsets of personnel who will be involved in the study. Trained by an array of specialists and investigators on the study, blinded adjudicators were sensitized to the need to collect independent and objective outcome data from enrolled subjects at the various time points of the study. In addition, all clinicians across all four sites of the study were brought up to speed with expectations and assigned tasks in the course of the study.

This study shall conduct a careful assessment of both benefits and costs of an innovative interventions as well as usual care for stroke survivors. It is expected that this study will provide data on the efficacy of the study tools. A successful implementation of the project would serve as a model of cost-effective quality stroke care for implementation in other countries in Sub Saharan Africa.

List of abbreviations

ABC	approximate bootstrap confidence
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BP	blood pressure
CBA	cost–benefit analysis
CEA	cost effectiveness analysis

CUA	cost utility analysis
GLMM	generalized linear mixed model
HRQOL	health-related quality of life
HRQOLISP	health-related quality of life in stroke patients
ICER	incremental cost-effectiveness ratio
LY	life years
NCC	National Communication Commission
NCDs	non-communicable diseases
QALYs	quality adjusted life years
RCT	random controlled trial
THRIVES	Tailored Hospital-based Risk Reduction to Impede Vascular Events after Stroke

Competing interests

Olanrewaju Olaniyan declares that he has no conflict of interest.
 Mayowa O. Owolabi declares that he has no conflict of interest.
 Rufus O. Akinyemi declares that he has no conflict of interest.
 Babatunde L. Salako, declares that he has no conflict of interest.
 Samantha Hurst declares that she has no conflict of interest.
 Oyedunni Arulogun declares that she has no conflict of interest.
 Mulugeta Gebregziabher declares that he has no conflict of interest.
 Ezinne Uvere, declares that she has no conflict of interest.
 Bruce Ovbiagele, declares that he has no conflict of interest.

Authors' contribution

OO takes a leading role in writing and finalizing of the manuscript. MOO and BO conceptualized and supervised the THRIVES study, contributed to the study design, made substantial contributions to quality assurance. MG contributed to the method and statistical analysis section. All authors have made substantial contributions to conception and design of the study protocol. All authors have given final approval of the version to be published. All authors read and approved the final manuscript.

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Acknowledgments

The study was supported by a research grant from National Institutes of Health (National Institute of Neurological Disorders and Stroke – Award Number U01 NS079179) and conducted as part of the Global Alliance for Chronic Diseases (GACD) initiative.

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