PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the economic evaluation of the China Salt Substitute and Stroke Study (SSaSS)
AUTHORS	Li, Ka-Chun; Tian, Maoyi; Neal, Bruce; Huang, Liping; Yu, Jie; Liu, Yishu; Yin, Xuejun; Zhang, Xinyi; Wu, Yangfeng; Li, Nicole; Elliott, Paul; Yan, Lijing; Labarthe, Darwin; Hao, Zhixin; Shi, JP; Feng, Xiangxian; Zhang, Jianxin; Zhang, Yuhong; Zhang, Ruijuan; Zhou, Bo; Li, Zhifang; Sun, Jixin; Zhao, Yi; Yu, Yan; Si, Lei; Lung, Thomas

VERSION 1 – REVIEW

REVIEWER	Leopold Aminde Non-communicable Disease Unit, Clinical Research Education, Networking & Consultancy
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	In this study protocol, Ka-Chun Li and colleagues plan to perform an economic evaluation of the China Salt Substitute and Stroke Study (cluster randomized controlled trial). The paper is well written, the case for the evaluation is made and the proposed study methods are for the most part well presented (although brief in some areas). I have a few questions for clarity: 1) Are there plans to extrapolate the findings beyond the trial period? e.g. a lifetime horizon using decision analytic modelling techniques, in order to capture the maximum possible benefits (and costs) that could accrue from this intervention, especially given the known long term issues associated with stroke such as disability, etc? 2) In terms of the perspective, stroke clearly has consequences like productivity losses both for the patient and for patient care-givers. Is there scope for approaching the analysis from a societal perspective (perhaps in sensitivity analysis) in order to capture these wider societal costs? 3) It does not seem immediately clear what willingness to pay threshold will be used to consider the intervention as cost-effective or not. Minor typo: Page 7, line 48: "...prior studies in rural China has proven that using salt substitutes..". I think that should read "..have proven.." Thank you.

REVIEWER	Roberto Longo University of Leeds, Academic Unit of Health Economics
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	The economic evaluation seems to have been planned at the end of the trial and for this reason the study design might encounter difficulties in answering the research question. Current guidelines for economic evaluation recommend to researchers to include health economics aspects from the conception of their intervention. For example, The Medical Research Guidelines in the UK, states that it is best to involve health economists early in the planning of design of the evaluation, so that the economic evaluation is fully integrated. The evaluation described in this protocol does not seem fully integrated. The authors themselves refer to one fundamental limitation with the collection of EQ-5D utilities: data were collected from a random subset (10% of clusters) of trial population during the 4 mid-term follow-ups. Another limitation, not mentioned upon, is the measurement of cost and outcomes. Routine data will be able to provide information on inpatient and outpatient care but no data collection was planned during the trial to supplement this info. How are the authors planning to identify and value primary and community care? The description of measure of cost and resource use is not sufficiently detailed to allow the study to be repeated; for e.g. timepoints for measurements are not specified, neither are the reference costs used to value the resource use.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments	Authors' response	Changes made to the manuscript
REVIEWER 1 In this study protocol, Ka-Chun Li and colleagues plan to perform an economic evaluation of the China Salt Substitute and Stroke Study (cluster randomized controlled trial). The paper is well written, the case for the evaluation is made and the proposed study methods are for the most part well presented (although brief in some areas). I have a few questions for clarity: Major points: 1. Are there plans to extrapolate the findings beyond the trial period? e.g. a lifetime horizon using decision analytic modelling techniques, in order to capture the maximum possible benefits (and costs) that could accrue from this intervention, especially given the known long term issues associated with stroke such as disability,	Thank you for your advice. The economic evaluation will focus on the trial period only, as this is the largest ever RCT (n=20,996) conducted to determine the effects of salt substitute on stroke events and mortality. In addition to the large sample size, the other major strengths include the comprehensive cost data collected using the routinely collected NCMS data and 5-year follow up. Given the trial population consists of those with a history of stroke (72.7%) and the lack of a validated secondary cardiovascular risk prediction model to predict further stroke, CVD events and CVD-related mortality, we believe conducting a within-trial analysis only to be the best course of action.	N.A.

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etc?		
2. In terms of the perspective, stroke clearly has consequences like productivity losses both for the patient and for patient care-givers. Is there scope for approaching the analysis from a societal perspective (perhaps in sensitivity analysis) in order to capture these wider societal costs?	Thank you. We agree with the reviewer that productivity losses both for the patient and for patient care-givers are an important consideration for people who suffer from stroke, however we did not capture the necessary data (Working status, income and informal/formal caregiver status post-stroke) to quantify this within the trial. Furthermore, the mean age of the participants was 65.4 years at baseline and the majority of them were already retired. Generally in rural China, women over the age of 50 or men over the age of 55 will start to receive pension automatically. Therefore, we have clarified the analysis will only focus on the healthcare system perspective rather than the wider societal one.	(Page-2 Line-14, Page-6 Line-15 and Page-7 Line-17) We changed: … from a "government" perspective to "healthcare system" perspective…
3. It does not seem immediately clear what willingness to pay threshold will be used to consider the intervention as cost-effective or not.	Thank you. There is currently no determined willingness-to-pay threshold in China. We have used 1*GDP per capita (10261.7 USD, 2019) as the WTP threshold reference which was recommended in the Chinese guidelines for Pharmacoeconomics in the base case analysis [1]. In addition, we will provide a range of WTP values and the probability of cost-effectiveness using a cost-effectiveness acceptability curve.	(Page-8 Line-7) We added: …depicted in a cost-effectiveness plane. "A cost-effectiveness acceptability curve will be presented to show the probability of cost-effectiveness of the bootstrapped samples for a range of willingness-to-pay values."
Minor points: Page 7, line 48: "...prior studies in rural China has proven that using salt substitutes..". I think that should read "..have proven.."	Thank you. We have corrected the typo.	(Page-4 Line-26) We changed:

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		"has" to "have".
REVIEWER 2 The economic evaluation seems to have been planned at the end of the trial and for this reason the study design might encounter difficulties in answering the research question. Current guidelines for economic evaluation recommend to researchers to include health economics aspects from the conception of their intervention. For example, The Medical Research Guidelines in the UK, states that it is best to involve health economists early in the planning of design of the evaluation, so that the economic evaluation is fully integrated. The evaluation described in this protocol does not seem fully integrated. Major points: 1. The authors themselves refer to one fundamental limitation with the collection of EQ-5D utilities: data were collected from a random subset (10% of clusters) of trial population during the 4 mid-term follow-ups.	Thank you for your comments. Whilst the EQ-5D data was collected from the beginning, as stated in the trial design article (Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS)—A large-scale cluster randomized controlled trial),[2] due to the limited recourses and operational difficulties in rural areas, we collected relevant data only on subsets of trial population. As stated in the paper, we agree with the reviewer that this is a potential limitation. However, to supplement the EQ-5D data collected, we will conduct a literature review of utility values in stroke patients and compare with the data collected in the trial population. This will inform our imputation strategy.	(Page-9 Line-5 to 6) We made the changes: Nevertheless, "the collected data will be compared with utility values from different sources of literature, which will inform the" imputation strategy "~~will be adopted~~" for participants without the data.
2. Another limitation, not mentioned upon, is the measurement of cost and outcomes. Routine data will be able to provide information on inpatient and outpatient care but no data collection was planned during the trial to supplement this info. How are the authors planning to identify and value primary and community care? The description of measure of cost and resource use is not sufficiently detailed to allow the study to be repeated; for e.g. timepoints for measurements	Thank you. We apologise that we didn't clarify the structure of the NCMS data clearly in the previous manuscript. Briefly, the NCMS data is the comprehensive data for all kinds of healthcare services at all levels (primary health care and above). Common data variables include patient identifiable information, date, health facility name, diagnosis and cost (total cost and out-of-pocket payment). The costs of service use will be estimated based on the NCMS data due to the lack of reference	(Page-7 Line-26 to 29) We added: …outpatient service was 55% and 50%, respectively. "Routinely collected data from the NCMS provides detailed information such as diagnosis, reimbursement and our-of-pocket payment for both inpatient and outpatient services at all levels." Each participant's aggregate service use cost "of relevant outcomes" will be valued

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are not specified, neither are the reference costs used to value the resource use.	cost in China. The data is retrospectively linked through the whole period of SSaSS trial. It is worth mentioning that, in rural China, many village clinics are limited in their ability to provide the first level of healthcare and fail to play the primary care role. As a result, most people received their treatments and medications mainly from the township hospitals. Despite of this, NCMS data also capture the healthcare cost provided at the primary health care levels – i.e. in this setting, the village clinics and township hospitals. Thus, we believe the routine data of NCMS system is the best data source available to date.	from… (Page-9 Line-1) We added: … the counterparts in a real-world setting. "Also, NCMS does not reach 100% coverage and participants may drop out from the NCMS. However, the missing events can be complemented by the face-to-face follow up." In addition…

VERSION 2 – REVIEW

REVIEWER	Leopold Aminde Non-communicable Disease Unit, Clinical Research Education, Networking & Consultancy
REVIEW RETURNED	22-Apr-2021

GENERAL COMMENTS	Authors have satisfactorily addressed my comments. Minor typo: Page 7, line 27: "...NCMS provides detailed information such as diagnosis, reimbursement and our-of-pocket payment for both inpatient and outpatient services at all levels." I think authors meant 'out-of-pocket' payment.. Thank you.

REVIEWER	Roberto Longo University of Leeds, Academic Unit of Health Economics
REVIEW RETURNED	20-May-2021

GENERAL COMMENTS	I was happy with the author's response to my comments and the changes applied to the manuscript as a consequence. Therefore I'd like to recommend the paper for publication.