

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for an economic evaluation alongside a cluster randomised controlled trial: cost-effectiveness of Learning Clubs, a multicomponent intervention to improve women's health and infant's health and development in Vietnam
AUTHORS	Nguyen, Trang; Sweeny, Kim; Tran, Thach; Luchters, Stanley; Hipgrave, David B.; Hanieh, Sarah; Tran, Tuan; Tran, Ha; Biggs, Beverley-Ann; Fisher, Jane

VERSION 1 - REVIEW

REVIEWER	Manuela Deidda University of Glasgow, UK
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	<p>This study protocol describes the planned economic evaluation of the 'Learning Club', a complex, public health intervention (PHI) directed towards the improvement of child health and the development of maternal mental health in Vietnam. Assessing whether this intervention has the potential to generate value for money is a key topic from a policy perspective, also in consideration of the wide-ranging and cross-sectoral consequences of such an intervention. Also, there is currently a lack of evidence regarding the value for money generated by early childhood interventions, especially in LIMCs.</p> <p>However, I think the protocol presents some major issues that I would like the authors to address in the revised version of the manuscript.</p> <p>1) This study has been designed to tackle the specificity of a PHI, including a societal perspective and a plethora of outcomes measuring different aspect of maternal and infant health and well-being. However, I think the protocol lacks an adequate discussion regarding the methodological challenges in the design and conducting of such a complex intervention. There is a vast literature on this topic (e.g. (Byford and Sefton, 2003;Smith and Petticrew, 2010) which can be referenced.</p> <p>2) The abstract should be self-explaining, including a) background information (i.e. importance of improving maternal and infant physical and mental health, especially in resource-constrained environments), b) a short description of the intervention, c) methods. The abstract does not include neither a) nor b), focusing exclusively on methods.</p>
-------------------------	--

	<p>3) The authors mention the complexity of the intervention in several instances. However, there is a lack of discussion regarding the challenges that such a complexity entails for the economic evaluation, such as multiple, intersectoral outcomes, complex causal pathways, spillovers. I suggest the authors to discuss how these challenges have been tackled in the planned economic evaluation. In general, the description of the planned economic evaluation of the 'Learning' intervention should be contextualized within the economic evaluation alongside complex PHIs.</p> <p>4) The paper provides little explanation of what the Learning Intervention involves. Also, it is not clear what is 'standard care'. I suggest the authors to include a table with a more detailed description of the intervention and the control (which treatments include, target population and relevant subgroups, timeline etc.).</p> <p>5) I suggest the authors to restructure the method section including two subsections: 'within trial' evaluation and 'long term'.</p> <p>6) The 'learning' intervention has the potential to have wide ranging, cross-sectoral short and long-term consequences. The authors plan to conduct a CEA and a CUA to address short term cost-effectiveness of the intervention, and a ROI to assess long-term value for money. In this regards, the ROI approach should be described in more details. e.g. the authors state on page 10 'the analysis compares the economic benefits of the interventions due to future workforce participation and productivity and savings and other costs..' which costs/cost savings? which time horizon is going to be adopted?</p> <p>7) I suggest the authors to include an economic evaluation logic model, describing the causal pathways of outcomes and resource use, over the short and long term.</p> <p>8) the conclusion section needs to be expanded including potential limitation of the economic evaluation (e.g. low literacy of study participants which can constrain the cost estimation, as mentioned in the 'strengths and limitations'), discussion of the challenges inherent to designing and conducting the economic evaluation alongside such a complex PHI etc.</p> <p>9) the study is a clustered RCT. The authors should explain how they plan to deal with the clustering of cost and outcomes by 'communes' (e.g. multilevel models).</p> <p>7) The authors should include a cost consequence analysis (CCA), which is recommended in case of complex PHI, where multiple benefits of the interventions are captured by multiple outcomes.</p> <p>8) table 2 should be more detailed, including sub-categories of costs (e.g. direct costs: medications; visits to GP etc.), as well as the unit of measure.</p> <p>9) do the authors plan to perform any subgroup analysis (e.g. by level of deprivation)? this intervention has the potential to have relevant implications from an equity perspective. This should be discussed.</p>
--	---

	<p>Byford, S., & Sefton, T. (2003). Economic evaluation of complex health and social care interventions. <i>National Institute Economic Review</i>, 186(1), 98-108.</p> <p>Smith, R. D., & Petticrew, M. (2010). Public health evaluation in the twenty-first century: time to see the wood as well as the trees. <i>Journal of Public Health</i>, 32(1), 2-7.</p>
--	--

REVIEWER	Vicki Brown Deakin University, Australia
REVIEW RETURNED	11-Jun-2019

GENERAL COMMENTS	<p>This sounds like a very interesting study, and I will look forward to reading the results of the trial in due course. However, this paper needs some refinement before it is ready for publication. The study design is reasonable, but several sections could use more detail added. Also, you have not included a section on strengths and limitations. There is also no mention of sensitivity analysis?</p> <p>Other comments follow:</p> <p>Abstract: Line 14: Missing words here? Sentence currently reads: "This economic evaluation will be conducted from a societal perspective alongside a cluster randomized controlled trial of the impact of the Learning." Line 15: 1,008 pregnant women</p> <p>Article summary: Please reword the first dot point. Second point: The study will collect (not the protocol). Also is the correct terminology Learning Club or Learning Clubs? (Within keywords you have no "s" on Club)</p> <p>Methods: Aim and objectives: Aim 2. Intervention, not interventions Aims 3 and 4 need ; Aim 4. Return not returns</p> <p>Setting: Line 37: The district health centre? Or: District health centres are... Line 38: Some districts may have a district..... Line 46: and was expected to cover 70%.....</p> <p>Study population and description of the intervention: Line 52: Here you call it the Learning Club project. Previously you had called it the Learning Club program. Suggest consistent terminology. How were pregnant women invited to participate?</p> <p>Sample size: How was sample size calculated? A brief sentence explaining would be beneficial here.</p> <p>Blinding:</p>
-------------------------	--

	<p>Line 22: Sentence “No information of intervention and control groups will be provided to the data collectors.” Could be more simply and clearly written.</p> <p>Health and development outcomes: Suggest not including underlining in this section. Can you be more explicit in stating the weight for height will be measured by data collectors.</p> <p>Line 50: The health-related quality of life of mothers..... Line 50: The EQ-5D-5L is a combination of quality of life and quantity of life? Not sure what you mean here. Also, why did you select this instrument? How is it scored? What value set will be used? How are you calculating utilities?</p> <p>Measurement of costs and valuation of costs: I would prefer that these two sections are combined, so that you describe the cost that you will measure and then immediately give detail of how it will be valued (including sources of data etc). You could use the heading: Identification, measurement and valuation of resource use.</p> <p>Line 39: Can you be more clear as to what you mean by household members? Also, you have already stated that you are taking a societal perspective. I suggest that you re-structure this section on measurement of costs, to have a paragraph per cost category that you present in Table 2. At the moment there is some repetition, and it is hard to follow as it seems to jump back and forwards between categories. How are you estimating travel costs? What is your source for health care cost data? Table 2 would be more informative if you added a column with descriptions of the various costs, or examples. For instance, “materials and supplies” is very broad and doesn’t really give much information.</p> <p>Economic evaluation: Are you calculating ICERs for the CUA? If so, suggest taking the text on calculation of ICERS from the CEA section and adding elsewhere. CUA section: This section needs more refinement. Can you provide a brief description of CUA, which would be helpful to non-health economist audiences? Be more direct in how you will calculate QALYs here. ROI: This section needs to provide more detail on the established modelling method you are using. Also, what value of a statistical life year are you using?</p> <p>Currency, price date and conversion Reference for IMF PPP’s?</p> <p>Discount rate Reference for discount rate? What lower and higher discount rates will you apply?</p> <p>Conclusion This is a long sentence. Suggest break into two.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Manuela Deidda

Institution and Country: University of Glasgow, UK

1. This study has been designed to tackle the specificity of a PHI, including a societal perspective and a plethora of outcomes measuring different aspect of maternal and infant health and well-being. However, I think the protocol lacks an adequate discussion regarding the methodological challenges in the design and conducting of such a complex intervention. There is a vast literature on this topic (e.g. (Byford and Sefton, 2003; Smith and Petticrew, 2010) which can be referenced.

Response:

We have revised the discussion. “It is challenging to conduct an economic evaluation of a complex public health intervention due to its diverse potential benefits to health and social sectors. Typically, a micro-level approach has been used and promoted among economic evaluations which mainly focused on calculating the cost effectiveness of a particular health or clinical outcome such as mortality rate. This method is not helpful for decision-makers taking into account the overall context (47, 57). The Learning Clubs program is a complex public health intervention which aims to address five main areas including macro and micro-nutrition; gender empowerment; men’s engagement in household work, women’s mental health; and child health and development (28). The program has complex causal pathway because it may have positive impacts at individual, family and community levels such as infant’s health and development; women’s health; family environment; and community empowerment and awareness. Therefore, a macro-level method is adopted by adding a cost-consequence analysis to the CEA and CUA in this protocol to capture all health or non-health outcomes. In the long term, the return on investment analysis provides policymakers in resource-constrained environments with an easily understood metric to prioritise health interventions in framing health budgets.”

28. Fisher J, Luchters S, Tran TD, Hipgrave D, Hanieh S, Tran H, et al. Addressing multiple modifiable risks through structured community-based Learning Clubs to improve maternal and infant health and infant development in rural Vietnam: protocol for a parallel group cluster randomised controlled trial. *BMJ Open*. 2018;8:e023539.

47. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The Role of Cost-Consequence Analysis in Healthcare Decision-Making. *Pharmacoeconomics*. 1998;13(3):277-88.

57. Byford S, Sefton T. Economic evaluation of complex health and social interventions. *National Institute Economic Review*. 2003;186 October:70-80.

2. The abstract should be self-explaining, including a) background information (i.e. importance of improving maternal and infant physical and mental health, especially in resource- constrained environments), b) a short description of the intervention, c) methods. The abstract does not include neither a) nor b), focusing exclusively on methods.

Response

Introduction

Economic evaluations of complex interventions in early child development are required to guide policy and program development, but few are yet available.

Methods and Analysis

Although significant gains have been made in maternal and child health in resource-constrained environments, this has mainly been concentrated on improving physical health. The Learning Clubs program addresses both physical and mental child and maternal health. This study is an economic evaluation of a cluster randomized controlled trial of the impact of the Learning Clubs program in Vietnam. It will be conducted from a societal perspective and aims to identify the cost-effectiveness and the economic and social returns of the intervention. A total of 1008 pregnant women recruited from 84 communes in a rural province in Vietnam will be included in the evaluation. Health and cost data will be gathered at three stages of the trial and used to calculate incremental cost-effectiveness ratios per percentage point improvement of infant's development, infant's health, and maternal common mental disorders expressed in quality-adjusted life years gained. The return on investment will be calculated based on improvements in productivity, the results being expressed as benefit-cost ratios.

3. The authors mention the complexity of the intervention in several instances. However, there is a lack of discussion regarding the challenges that such a complexity entails for the economic evaluation, such as multiple, intersectoral outcomes, complex causal pathways, spillovers. I suggest the authors to discuss how these challenges have been tackled in the planned economic evaluation. In general, the description of the planned economic evaluation of the 'Learning' intervention should be contextualized within the economic evaluation alongside complex PHIs.

Response

We have addressed these comments on the discussion. Please refer to the first comment for detail.

4. The paper provides little explanation of what the Learning Intervention involves. Also, it is not clear what is 'standard care'. I suggest the authors to include a table with a more detailed description of the intervention and the control (which treatments include, target population and relevant subgroups, timeline etc.).

Response:

We have revised the background:

“Learning Clubs for Women’s Health and Infant Health and Development is an innovative multi-component psychoeducational intervention designed to improve the physical and mental health of women and the health and development of their infants in a resource-constrained setting, by addressing multiple risks at the same time. Its impact is being established in a two-arm parallel group cluster randomized controlled trial being conducted in 84 communes in a rural province in Vietnam in which 42 communes are assigned randomly to receive the intervention in 2018. All women in the trial receive pregnancy and child health care services from commune health stations including free pregnancy checks, giving birth in commune health stations (if the hospital is too far and the commune health station is qualified for birth assistance) or hospitals nearby, National Growth Monitoring and

Expanded Immunisation Programs (hereafter referred to as the usual standard of care). Women in the intervention group are invited to participate in Learning Clubs, which comprise facilitated small groups which meet in the commune at fortnightly intervals and provide perinatal stage-specific information and learning activities from pregnancy to one year postpartum. The intervention draws on content from interventions demonstrated to be effective in addressing at least one risk in a resource-constrained setting and includes five main components: macro- and micro-nutrition for women and infants, gender empowerment, strengthening the intimate partner relationship, women's mental health, and providing sensitive, responsive care for infants. Learning Clubs are designed to be facilitated at the primary care level by members of the Women's Union with support from the local health and education sectors. The intervention is to be offered in eight sessions during pregnancy, and a combination of eleven sessions and one home visit in the first year after giving birth. The Learning Clubs program is described in detail elsewhere (28)."

28. Fisher J, Luchters S, Tran TD, Hipgrave D, Hanieh S, Tran H, et al. Addressing multiple modifiable risks through structured community-based Learning Clubs to improve maternal and infant health and infant development in rural Vietnam: protocol for a parallel group cluster randomised controlled trial. *BMJ Open*. 2018;8:e023539.

5. I suggest the authors to restructure the method section including two subsections: 'within trial' evaluation and 'long term'.

Response

We have made these amendments as requested

6. The 'learning' intervention has the potential to have wide ranging, cross-sectoral short and long-term consequences. The authors plan to conduct a CEA and a CUA to address short term cost-effectiveness of the intervention, and a ROI to assess long-term value for money. In this regards, the ROI approach should be described in more details. e.g. the authors state on page 10 'the analysis compares the economic benefits of the interventions due to future workforce participation and productivity and savings and other costs.' which costs/cost savings? which time horizon is going to be adopted?

Response

We have revised the description of the Return on investment analysis

"The investment case for the intervention will be assessed by calculating the return on investment using a validated, peer-reviewed modelling approach which has been applied in studies on reproductive, maternal, newborn and child health (48); stillbirths (49); mental health (50); adolescent health and wellbeing (51) and cardiovascular disease (48-52).

This analysis calculates the economic benefits of the intervention arising from mortality and morbidity averted due to the Learning Clubs program. These benefits occur over the working lives of the participants due to increase workforce participation and improved productivity. Savings from health expenditure averted are also included as benefits. These benefits are compared to the cost of the intervention incurred by the Government and participants. The social return on investment can also be calculated using standard measures of the value of a statistical life year such as the "full income" approach for low and middle income countries (53)."

48. Bertram MY, Sweeny K, Lauer JA, Chisholm D, Sheehan P, Rasmussen B, et al. Investing in non-communicable diseases: an estimation of the return on investment for prevention and treatment services. *The Lancet*. 2018.

49. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *The Lancet Psychiatry* 2016;3(5):415-24.

50. Sheehan P, Sweeny K, Rasmussen B, Wils A, Friedman HS, Mahon J, et al. Building the foundations for sustainable development: A case for global investment in the capabilities of adolescents. *The Lancet*. 2017.

51. Stenberg K, Axelson H, Sheehan P, Anderson I, Gülmezoglu AM, Temmerman M, et al. Advancing social and economic development by investing in women's and children's health: a new Global Investment Framework. *The Lancet*. 2014;383(9925):1333-54.

52. Hoop-Bender Pt, Stenberg K, Sweeny K. Reductions in stillbirths—more than a triple return on investment. *The Lancet*. 2016;387(10018):e14-e6.

53. Jamison DT, Summers LH, Alleyne G, Arrow KJ, Berkley S, Binagwaho A, et al. Global health 2035: a world converging within a generation. *The Lancet*. 2013;382:1898-955.

7. I suggest the authors to include an economic evaluation logic model, describing the causal pathways of outcomes and resource use, over the short and long term.

Response

We have developed an economic evaluation logic model (figure 1) as suggested.

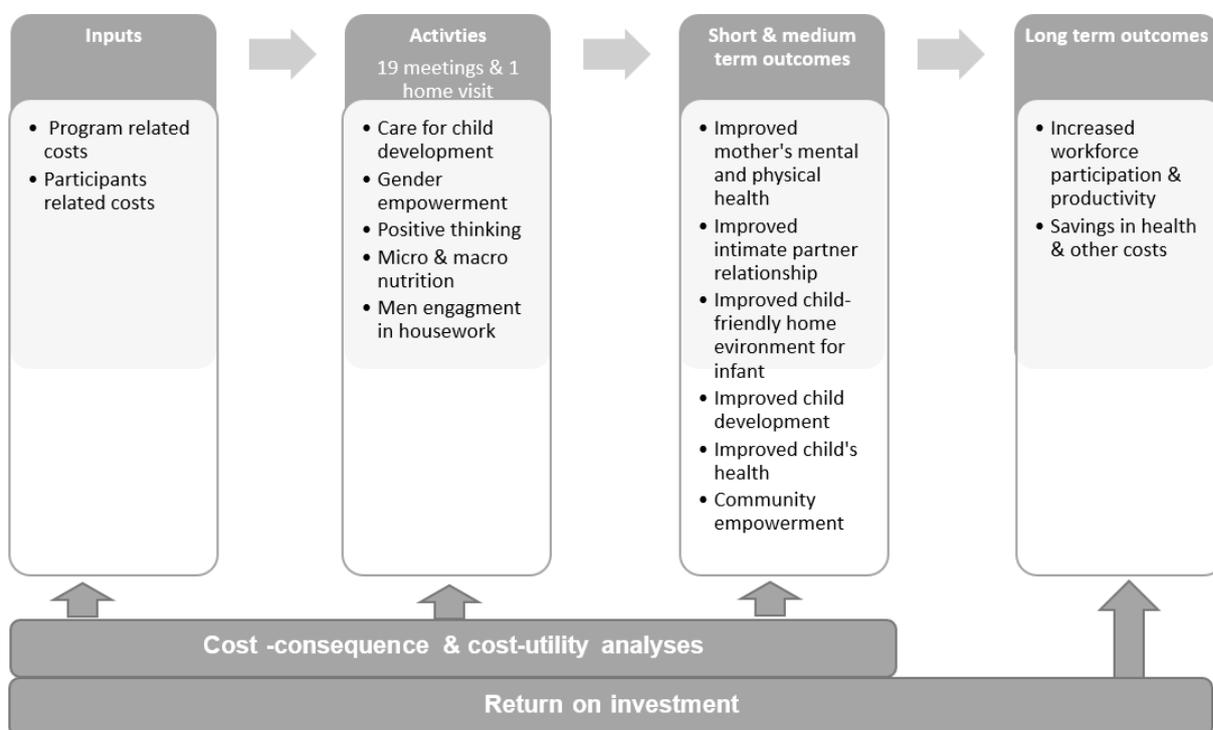


Figure 1 -Economic evaluation logic model

8. the conclusion section needs to be expanded including potential limitation of the economic evaluation (e.g. low literacy of study participants which can constrain the cost estimation, as

mentioned in the 'strengths and limitations'), discussion of the challenges inherent to designing and conducting the economic evaluation alongside such a complex PHI etc.

Response

We have revised the conclusions as suggested.

“Despite the potential limitation in the estimates of Learning Clubs participants’ costs and the complexity of the Learning Clubs program, the economic evaluation is designed with careful consideration of these factors. It is expected that the economic evaluation will provide evidence of the cost and benefits of a first-ever comprehensive intervention for ECD in a LMICs. In addition, the evaluation will inform policymakers about the relative value for money of the Learning Clubs program at the provincial level and the likely indicators for scaling nationwide.”

9. the study is a clustered RCT. The authors should explain how they plan to deal with the clustering of cost and outcomes by 'communes' (e.g. multilevel models).

Response

We have revised the analytical method

“A multilevel model approach will be used for data analyses to address missing data, cost skewness and the difference of costs among clusters (56). Baseline variables will be included in the regression models of costs and outcomes to adjust the difference between control and intervention groups, and other sociodemographic characteristics such as economic status, educational level, occupation. For non-normal distribution of continuous costs and outcomes (such as quality of life among mothers and the BSID score of children), a generalized linear regression will be employed in STATA version 13 (StataCorp LP, College Station, Texas, USA). Logit model will be used for binary outcomes (having common mental disorders, and infant wasting). Parameter uncertainty will be addressed by deterministic and probabilistic sensitivity analysis (44).”

44. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied Methods of Cost-effectiveness Analysis in Health Care United Kingdom Oxford University Press 2011.

56. Ng ES-W, Diaz-Ordaz K, Grieve R, Nixon RM, Thompson SG, Carpenter JR. Multilevel models for cost-effectiveness analyses that use cluster randomised trial data: An approach to model choice. *Statistical Methods in Medical Research*. 2016;25(5):2036-52.

10. The authors should include a cost consequence analysis (CCA), which is recommended in case of complex PHI, where multiple benefits of the interventions are captured by multiple outcomes.

Response

We have revised the design as requested.

“The protocol was developed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Guideline (30). The economic evaluation will include cost-effectiveness, cost-consequence and cost-utility analyses from the health provider and societal perspectives as well as an analysis of the economic and social return on investment.”

In addition, more secondary outcomes are added such as indicators of infant’s health, women’s health, family environment; and community empowerment and awareness. These changes are illustrated in the table 1.

Table 1: Overview of outcome measures

Measure	Means of collection	Timing of collection	Source of data
Infant's development – primary outcome			
Cognitive development	BSID, 3rd Ed	Follow up 3	Direct child assessment
Language development			
Motor development			
Social-emotional development			
Secondary outcomes			
Infant's health			
Infant's wasting	Mother–infant scale (Seca 876); portable stadiometers & length boards (ShorrBoard)	Follow-up 3	Direct child measurement
Antibiotic use	Study specific questions	Follow up 2 & 3	Main caregivers
Exclusive breast feeding			
Common illness symptoms in the previous two weeks			
Inpatient service use			
Outpatient service use			
Women's health			
Quality of Life	EQ-5D-5L	Baseline, Follow-up 3	Structured interview with women
Maternal common mental disorders	DASS-V	Baseline, Follow-up 3	Structured interview with women
Productivity change of mothers	WPAI-GH	Baseline, follow-up 3	Structured interview with women
Absenteeism from work due to child health	Study specific questions	Follow up 2, and follow-up 3	Structured interview with women
Family environment			
Home environment for infant development	HOME Inventory	Follow up 2, and follow-up 3	Semi-structured observation and parent interview at home.
Intimate partner relationship	IBM-V	Baseline, Follow-up 2, Follow-up 3	Questionnaire interview with women

Measure	Means of collection	Timing of collection	Source of data
Domestic violence against women	WHO Multi-Country Study on Women's Health and Domestic Violence Questionnaire	Baseline, Follow-up 2, Follow-up 3	Questionnaire interview with women
Household tasks sharing from the husband	Study specific questions	Follow up 2, and follow-up 3	Questionnaire interview with women
Child's caring support from the husband			
Emotional care from the husband to the wife			
Community empowerment and awareness			
Number of social organizations integrated child care messages in their routine meetings	Study specific questions	Baseline, Follow-up 2, Follow-up 3	Self-administered questionnaire sent to commune facilitators
Change of knowledge of Head of the commune authority			
Child care propaganda through loudspeakers at each commune			

30. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value in Health* 2013;16:231-50.

11. table 2 should be more detailed, including sub-categories of costs (e.g. direct costs: medications; visits to GP etc.), as well as the unit of measure.

Response

We have revised the table 2 as requested.

Table 2: Cost categories in the cost analysis

Cost component	Description	Means of collection	Source of data	Timing of collection
Program related costs				
Personnel (staff and consultants)	<ul style="list-style-type: none"> Staff salary Consultant fee 	CostIt Software version 4.5	Financial & administrative records	Every three months
Materials and supplies	<ul style="list-style-type: none"> Participant manuals Facilitator manuals Posters Videos 			

Cost component	Description	Means of collection	Source of data	Timing of collection
Equipment operating costs	<ul style="list-style-type: none"> Office rent Stationery 			
Media and Policy advocacy operating costs	<ul style="list-style-type: none"> Workshops Study tour for journalists 			
Training & transportation operating costs	<ul style="list-style-type: none"> Training courses for provincial trainers Training courses for commune facilitators Supervision trips 			
Learning Clubs participants' costs				
Costs of health service use for mothers or children				
Direct medical costs	<ul style="list-style-type: none"> Drugs Physician visits Hospital stays Others 	Face-to-face interview	<ul style="list-style-type: none"> Study women Husbands, Grand-parents Other caregivers 	Follow-up 1, 2, 3
Direct nonmedical care costs	<ul style="list-style-type: none"> Transportation Equipment Accommodation Food Other out-pocket payments 			
Indirect resource use	<ul style="list-style-type: none"> Time missed from work for patient Time missed from work for unpaid caregiver 			
Costs of participating Learning Clubs meetings				
Indirect resource use	<ul style="list-style-type: none"> Travelling time Time missed from work for participant Travelling costs 	Face-to-face interview	<ul style="list-style-type: none"> Study women Family members 	Follow-up 1, 2, 3

Reviewer: 2

Reviewer Name: Vicki Brown

Institution and Country: Deakin University, Australia

1. Abstract:

Line 14: Missing words here? Sentence currently reads: "This economic evaluation will be conducted from a societal perspective alongside a cluster randomized controlled trial of the impact of the Learning."

Line 15: 1,008 pregnant women

Response

We have revised the abstract to provide further information.

"Although significant gains have been made in maternal and child health in resource-constrained environments, this has mainly been concentrated on improving physical health. The Learning Clubs program addresses both physical and mental child and maternal health. This study is an economic evaluation of a cluster randomized controlled trial of the impact of the Learning Clubs program in Vietnam. It will be conducted from a societal perspective and aims to identify the cost-effectiveness and the economic and social returns of the intervention. A total of 1,008 pregnant women recruited from 84 communes in a rural province in Vietnam will be included in the evaluation. Health and cost data will be gathered at three stages of the trial and used to calculate incremental cost-effectiveness ratios per percentage point improvement of infant's development, infant's health, and maternal common mental disorders expressed in quality-adjusted life years gained. The return on investment will be calculated based on improvements in productivity, the results being expressed as benefit-cost ratios."

2. Article summary:

Please reword the first dot point.

Second point: The study will collect (not the protocol). Also, is the correct terminology Learning Club or Learning Clubs? (Within keywords you have no "s" on Club)

Response

We have made these amendments in the article summary as requested.

- This study will contribute one of the first economic evaluations of a complex intervention to improve early child development in a resource-constrained setting.
- The study will use a societal perspective to collect the costs of health service use and to productivity of participation in the Learning Clubs program.
- Cost-consequences will be adopted to obtain secondary outcomes, including infant's health and development; women's health; family environment; and community empowerment and awareness.
- Learning Clubs program is multi-component intervention; hence it is difficult to capture the health and social benefits of each component
- Cost estimation of health service use may be constrained by low literacy among study participants.

3. Methods: Aim and objectives:
Aim 2. Intervention, not interventions
Aims 3 and 4 need;
Aim 4. Return not returns

Response

We have made these amendments in the methods as requested.

4. Setting:
Line 37: The district health centre? Or: District health centres are...
Line 38: Some districts may have a district.....
Line 46: and was expected to cover 70%

Response

We have revised these sentences in the setting section as requested.

5. Study population and description of the intervention:
Line 52: Here you call it the Learning Club project. Previously you had called it the Learning Club program. Suggest consistent terminology.
How were pregnant women invited to participate?

Response

We have made amendments to use Learning Clubs program consistently.

Under the section "Study population and sample size", we have added the recruitment method. "All pregnant women less than 20 gestational weeks who live in the selected communes, are invited to participate by commune health staff and village health workers. Women having cognitive or serious physical disability are not recruited in the study."

6. Sample size:
How was sample size calculated? A brief sentence explaining would be beneficial here.

Response

We have added the sample size calculation under the section "Study population and sample size". "The sample size is calculated to detect a difference in the infant's development (8% in the intervention group and 15% in the control group) with 80% statistical power and a significance level of 0.05, and intra-cluster correlation coefficient =0.03."

7. Blinding:
Line 22: Sentence "No information of intervention and control groups will be provided to the data collectors." Could be more simply and clearly written.

Response

We have revised the sentence. "Independent data collectors from the Hanam provincial Center for Disease Control will be trained by Hanoi Research and Training Center for Community Development

(RTCCD). They will collect data at baseline and three follow-up surveys. Data collectors are blinded to intervention allocation”.

8. Health and development outcomes:

Suggest not including underlining in this section.

Can you be more explicit in stating the weight for height will be measured by data collectors.

Line 50: The health-related quality of life of mothers.....

Line 50: The EQ-5D-5L is a combination of quality of life and quantity of life? Not sure what you mean here. Also, why did you select this instrument? How is it scored? What value set will be used? How are you calculating utilities?

Response

We have revised the sentences as requested.

“Infant wasting is assessed by data collectors to collect the weight, and height of the children. The weight for height ratio will be based on the child’s age in months and sex (34)”

“The health-related quality of life of mothers will be assessed by EQ-5D-5L which is a common questionnaire which was validated in Vietnam to measure generic health status due to its high sensitivity and specificity. The questionnaire has two parts: Part 1 consists of five questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels ranging from no problems to severe problems. Part 2 is an analogue scale which asks participants to report their health status. The scale ranges from "best imaginable health state" to "worst imaginable state" (35).”

9. Measurement of costs and valuation of costs:

I would prefer that these two sections are combined, so that you describe the cost that you will measure and then immediately give detail of how it will be valued (including sources of data etc). You could use the heading: Identification, measurement and valuation of resource use.

Response

We have made these amendments as requested.

10. Line 39: Can you be clearer as to what you mean by household members? Also, you have already stated that you are taking a societal perspective.

I suggest that you re-structure this section on measurement of costs, to have a paragraph per cost category that you present in Table 2. At the moment there is some repetition, and it is hard to follow as it seems to jump back and forwards between categories.

How are you estimating travel costs? What is your source for health care cost data?

Response

We have made these amendments as requested and revised the table 2.

Table 2: Cost categories in the cost analysis

Cost component	Description	Means of collection	Source of data	Timing of collection
Program related costs				
Personnel (staff and consultants)	<ul style="list-style-type: none"> • Staff salary • Consultant fee 	CostIt Software version 4.5	Financial & administrative records	Every three months
Materials and supplies	<ul style="list-style-type: none"> • Participant manuals • Facilitator manuals • Posters • Videos • Others 			
Equipment operating costs	<ul style="list-style-type: none"> • Office rent • Stationery 			
Media and Policy advocacy operating costs	<ul style="list-style-type: none"> • Workshops • Study tour for journalists 			
Training & transportation operating costs	<ul style="list-style-type: none"> • Training courses for provincial trainers • Training courses for commune facilitators • Supervision trips 			
Learning Clubs participants' costs				
Costs of health service use for mothers or children				
Direct medical costs	<ul style="list-style-type: none"> • Drugs • Physician visits • Hospital stays • Others 	Face-to-face interview	<ul style="list-style-type: none"> • Study women • Husbands, • Grand-parents • Other caregivers 	Follow-up 1, 2, 3
Direct nonmedical care costs	<ul style="list-style-type: none"> • Transportation • Equipment • Accommodation • Food • Other out-pocket payments 			
Indirect resource use	<ul style="list-style-type: none"> • Time missed from work for patient • Time missed from work for unpaid caregiver 			

Cost component	Description	Means of collection	Source of data	Timing of collection
Costs of participating Learning Clubs meetings				
Indirect resource use	<ul style="list-style-type: none"> • Travelling time • Time missed from work for participant • Travelling costs 	Face-to-face interview	<ul style="list-style-type: none"> • Study women • Family members 	Follow-up 1, 2, 3

In terms of the travel cost: “There is no postcode in Vietnam, therefore, using postcode for estimating travel expense is not feasible. In addition, the distance from participants’ house to the meeting venue is not far, hence the traveling cost will be calculated by self-reports.”

11. Table 2 would be more informative if you added a column with descriptions of the various costs, or examples. For instance, “materials and supplies” is very broad and doesn’t really give much information.

Response

We have made these amendments as requested.

12. Economic evaluation:

Are you calculating ICERs for the CUA? If so, suggest taking the text on calculation of ICERS from the CEA section and adding elsewhere.

Response

We have added the calculation to these sections.

CUA section: This section needs more refinement. Can you provide a brief description of CUA, which would be helpful to non-health economist audiences? Be more direct in how you will calculate QALYs here.

Response

The cost-utility analysis measures the incremental cost of achieving the health outcomes when they are measured using a common metric such as quality-adjusted life years (QALYs).

Using EQ-5D-5L, respondents make choices for each domain and their health status in a 1-digit number. Then these numbers will be combined in a 5-digit number which can be converted into a utility weight. Each of the health outcomes will be expressed in QALYs so that the total QALYs can be calculated for both the intervention and control groups. These total QALYS can then be divided by the costs for each group and the difference in QALYS per unit of cost can be compared (29). In this protocol, the incremental cost will be calculated with the difference in QALYs of study women.

29. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes Fourth Edition ed. United Kingdom Oxford University Press 2015.

ROI: This section needs to provide more detail on the established modelling method you are using. Also, what value of a statistical life year are you using?

Response

We have revised the economic evaluation section.

The investment case for the intervention will be assessed by calculating the return on investment using a validated, peer-reviewed modelling approach which has been applied in studies on reproductive, maternal, newborn and child health (48); stillbirths (49); mental health (50); adolescent health and wellbeing (51) and cardiovascular disease (48-52).

This analysis calculates the economic benefits of the intervention arising from mortality and morbidity averted due to the Learning Clubs program. These benefits occur over the working lives of the participants due to increase workforce participation and improved productivity. Savings from health expenditure averted are also included as benefits. These benefits are compared to the cost of the intervention incurred by the Government and participants. The social return on investment can also be calculated using standard measures of the value of a statistical life year such as the “full income “ approach for low and middle income countries (53).

48. Bertram MY, Sweeny K, Lauer JA, Chisholm D, Sheehan P, Rasmussen B, et al. Investing in non-communicable diseases: an estimation of the return on investment for prevention and treatment services. *The Lancet*. 2018.

49. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *The Lancet Psychiatry* 2016;3(5):415-24.

50. Sheehan P, Sweeny K, Rasmussen B, Wils A, Friedman HS, Mahon J, et al. Building the foundations for sustainable development: A case for global investment in the capabilities of adolescents. *The Lancet*. 2017.

51. Stenberg K, Axelson H, Sheehan P, Anderson I, Gülmezoglu AM, Temmerman M, et al. Advancing social and economic development by investing in women’s and children’s health: a new Global Investment Framework. *The Lancet*. 2014;383(9925):1333-54.

52. Hoop-Bender Pt, Stenberg K, Sweeny K. Reductions in stillbirths—more than a triple return on investment. *The Lancet*. 2016;387(10018):e14-e6.

53. Jamison DT, Summers LH, Alleyne G, Arrow KJ, Berkley S, Binagwaho A, et al. Global health 2035: a world converging within a generation. *The Lancet*. 2013;382:1898-955.

13. Currency, price date and conversion
Reference for IMF PPP’s?

Response

I have made the amendment as suggested.

14. Discount rate

Reference for discount rate? What lower and higher discount rates will you apply?

Response

I have made the amendment as suggested. "Where applicable, benefits and cost will be discounted at the standard World Bank and WHO-CHOICE rate of 3% (54). Sensitivity analysis will be undertaken with alternative rates."

15. Conclusion

This is a long sentence. Suggest break into two.

Response

I have made the amendment as suggested.

VERSION 2 – REVIEW

REVIEWER	Manuela Deidda University of Glasgow
REVIEW RETURNED	05-Oct-2019

GENERAL COMMENTS	<p>I think the authors have addressed satisfactorily all my comments. I only have few further comments that I would like to be addressed before the paper is publishable.</p> <p>1) From the latest EQ5D-5L documentation, it seems that EQ-5D-5L value set are not available for Vietnam. Do the authors intend to use the 'cross-walk' value set?</p> <p>2) the authors state ' The cost of informal care will be calculated by the total time spent by caregivers, away from income-generating work'. The authors should explain how they are going to valueate this time, i.e. which 'value' or unit cost are going to use to valueate informal care.</p>
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Manuela Deidda

Institution and Country: University of Glasgow

1. From the latest EQ5D-5L documentation, it seems that EQ-5D-5L value set are not available for Vietnam. Do the authors intend to use the 'cross-walk' value set?

Response

We have revised the description of the Methods section to provide further information.

“The health-related quality of life of mothers will be assessed by EQ-5D-5L which is a common questionnaire which was validated in Vietnam to measure generic health status among specific and general populations (35-37). The EQ-5D-5L value set for Vietnam is not available, so we will use the cross-walk value for Thailand, a neighbouring country that is both geographically and culturally close to Vietnam (38).”

35. Nguyen LH, Tran BX, Le QNH, Tran TT, Latkin CA. Quality of life profile of general Vietnamese population using EQ-5D-5L. *Health and Quality of Life Outcomes*. 2017;15:199.

36. Tran BX, Ohinmaa A, Nguyen LT. Quality of life profile and psychometric properties of the EQ-5D-5L in HIV/AIDS patients. *Health and Quality of Life Outcomes*. 2012;10:132.

37. Tran BX, Nguyen LH, Nong VM, Nguyen CT. Health status and health service utilization in remote and mountainous areas in Vietnam. *Health and Quality of Life Outcomes*. 2016;14:85.

38. Pattanaphesaj J, Thavorncharoensap M, Ramos-Goñi JM, Tongsiri S, Ingsrisawang L, Teerawattananon Y. The EQ-5D-5L Valuation study in Thailand. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2018.

2. The authors state 'The cost of informal care will be calculated by the total time spent by caregivers, away from income-generating work'. The authors should explain how they are going to value this time, i.e. which 'value' or unit cost are going to use to value informal care.

Response

We have revised the description of the Methods section to provide further information.

“The cost of informal care will be calculated by multiplying the total time spent by the caregiver away from income-generating work and the market wage rate of the informal caregiver using the opportunity cost method (49).”

49. Koopmanschap MA, Exel JNA, Berg Bvd, Brouwer WBF. An Overview of Methods and Applications to Value Informal Care in Economic Evaluations of Healthcare. *Pharmacoeconomics*. 2008;26(4):269-80.

VERSION 3 – REVIEW

REVIEWER	Manuela Deidda University of Glasgow, UK
REVIEW RETURNED	09-Oct-2019

GENERAL COMMENTS	The authors have addressed satisfactorily my comments.
-------------------------	--