PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol: Leveraging ongoing research to evaluate the health impacts of South Africa's salt reduction strategy, a prospective nested cohort within the WHO-SAGE multi-country, longitudinal study.
AUTHORS	Charlton, Karen; Ware, Lisa; Menyanu, Elias; Biritwum, Richard; Naidoo, Nirmala; Pieterse, Chiné; Madurai, Lorna; Baumgartner, Jeannine; Asare, George; Thiele, Elizabeth; Schutte, Aletta; Kowal, Paul

VERSION 1 - REVIEW

REVIEWER	David Watkins University of Cape Town, South Africa University of Washington, USA
REVIEW RETURNED	18-Jul-2016

GENERAL COMMENTS	This is a timely and much-needed study. There were an estimated 3.7 million deaths worldwide in 2013 that were attributable, at least in part, to excess dietary sodium (Global Burden of Disease 2013 Study). This included 10,300 deaths in South Africa and 2900 deaths in Ghana. South Africa's government is a leader among LMICs in taking steps to reduce population salt intake, but an independent evaluation of the policy is needed. This study fills that gap. In general, I think the authors have designed an excellent study that contains several very important objectives. I have three comments that I have classified as "major revisions" simply because they are cross-cutting to the entire study design and objectives - however, I do not think the authors need to go back to the drawing board; I am just recommending some changes, clarifications, and elaborations. Comment 1: Presentation I do think that the presentation of these 5 objectives could be improved especially in light of the stated aim of evaluating the effectiveness of the SA salt policy. To my read, objective 1 (baseline measurement) has already been completed, including urine collection, and if that is the case, it is not necessary to present this as part of the study protocol. (It would just be described in the Methods of the final manuscript(s)). The follow-up measurement will also happen "automatically" as part of SAGE, however, since this is part of the prospective study protocol, the methods for BP, urine, etc could be presented here. The core of this project seems to be a pre- and post- assessment of population blood pressure and the independent association of this

	with reduced sodium intake (estimated by urinary excretion and self-reported intake). A crucial part of this is the comparison with Ghana, the data from which I imagine would be pooled in the final analysis (see below). As a substudy, the authors will want to do objectives #2-3, which will provide insight into mechanisms and validate the use of proxy measures (eg spot urine and self-reported salt intake). I suggest the authors re-work this paragraph to frame their objectives more clearly for the casual reader. Again, I think the authors should stress that this is a policy impact evaluation study with a nested path/biochemical substudy (objectives 2-3) Comment 2: Conceptual model for evaluation, consideration of mixed methods I think this study, as primarily an assessment of policy effectiveness, would benefit from an additional figure and discussion of the overarching conceptual model of how that effectiveness will be demonstrated. I am thinking specifically of the approaches used in the M&E community and the methods presented, eg, in the World Bank handbook "Impact Evaluation in Practice" (Gertler et al, see especially ch 2). For instance, using an "inputs, outputs, outcomes, impact" framework as a Figure 1, the authors might outline that they are measuring changes in inputs (regulations and education) that lead to outputs (reduced bread salt and reduced discretionary salt use; also reduced urinary sodium) that lead to outcomes (reduced blood pressure) and eventually impact (incident and fatal CVD). The latter (CVD) may be difficult to incorporate because of the anticipated lag between BP change and CVD events, and the sample size may not be adequate if there is just one wave of follow-up. Perhaps the authors could advocate for more than 1 wave of follow-up to see if there are any hard CV changes? (That would increase the effective sample size for detecting CVD though it might not be part of WHO's plans.) Another aspect of M&E is the consideration of whether mixed methods are needed. In this case, the authors might consider doing in-depth interviews with stakeholders in government and industry as well as SAGE participants to see, over time, how the policy changes are being perceived - and whether they are being rolled out at all! This would be important corroborating information for the urinary sodium and BP data analysis -- without explicitly incorporating evidence that the policy is changing practices, the bio/clinical data could be criticized as simply reflecting secular trends. (The inclusion of Ghana data would not mitigate this - you still need some evidence that the policy is actually being exectued.) Comment 3: Comparing countries The objective on Ghana-South Africa comparisons is, in my view, the weakest aspect of the protocol. Care should be taken to address how this analysis will be done. There are several approaches: a. Simple comparison of means in SA and Ghana pre- and post-policy. Easiest to understand, but does not take into account confounders. b. Difference-in-differences analysis. This would be a multivariate linear regression on BP vs. salt excretion/intake in the pooled sample, with dummy variables for post and South Africa and an interaction term (whose coefficient would be the item of interest). Other confounders like age and sex could also be incorporated. c. Matching. If the SA and Ghana samples were felt to be too different (demographics, disease profile, etc) to pool completely as in (b), then a subset of Ghana patients could be matched (with

	replacement) as controls to the SA sample. The regression model might, instead of pre- and post- measurements, just calculate individual-level change in BP and sodium and do a (quasi) cross-sectional analysis of this variable. This method would be inferior to (b) but may be more feasible. If the authors do not feel comfortable carrying out this analysis themselves, I think it would be helpful to recruit a statistician or economist on the team who has experience in quantitative impact evaluation. Finally, I do not have any specific comments on the methods for biochemical and clinical variable measurement. All this seems appropriate to me. I look forward to reading the revised manuscript.

REVIEWER	Jennifer Poti University of North Carolina at Chapel Hill, USA
REVIEW RETURNED	15-Aug-2016

GENERAL COMMENTS	Major Comments: Thank you for the opportunity to review the manuscript entitled "Study Protocol: Evaluating the effectiveness of South Africa's salt reduction strategy, a natural experiment comparing South Africa with Ghana." The study uses urinary sodium measures to compare pre- and post-legislation sodium levels in a subsample of the WHO's SAGE in South Africa and uses a natural experiment design to compare these changes to those among a subsample in Ghana (with no sodium legislation). The manuscript is well-written and provides strong, clear motivation for this study. Minor revisions are needed to better justify the comparison to Ghana and explain the post-legislation measures. With revisions, this paper has great potential to provide valuable documentation describing much-needed evaluation of legislative approaches for population sodium reduction. Introduction Page 4, Lines 26-37: It would be helpful to provide more details about the legislation in South Africa, such as what foods have mandatory sodium targets (consider moving this from the Discussion to the Introduction). It would also be helpful to mention how much salt intake comes from processed food and from salt added during food preparation or at the table in South Africa. Pages 4 Line 59 – Page 5 Lines 1-4: Are there other efforts to evaluate the impact of the sodium legislation in South Africa? Methods Page 5, Lines 50-52: Please clarify the timing of the different waves of data collection, and specify which waves will be used in the sodium evaluation. Could you also add here information about how many waves are planned in the future? Page 5, Lines 52-57: How many respondents were included in Ghana, and what was their age distribution?

	Page 6, Lines 8 -20: Consider moving these sentences about the categories of households to the end of the paragraph. Clarify why the sampling strategy accounted for attrition, if all wave 1 households were included in wave 2; was there attrition? Page 6, Lines 46-52: Please provide more details about how the subsample of households was selected to provide urine samples. Page 6, Lines 55-59: Provide more explanation about why the years of data collection were not the same and did not even overlap for South Africa and Ghana. Please note in the discussion whether this might have an impact of the comparison of sodium changes in these 2 countries. Page 7, Lines 1-3: How was the subsample selected? Page 8, Lines 35-37: Is this the primary reason for not using PABA because of the participants' age range, or is it also because of the reasons mentioned in the WHO/PAHO guidelines about compliance or testing? Page 10, Line 5: What data will be collected in wave 3 (and beyond) to assess sodium or blood pressure post-legislation? Discussion Page 12, Lines 14-22: Consider mentioning that this study cannot determine the impact of legislation on younger populations or individuals without hypertension. Page 12, Line 42: What is meant by "economic modelling"? Please clarify. Page 12, Line 47-49: This paper is establishing the study protocol, so please add a more detailed examination and discussion of whether Ghana is a valid comparison population for South Africa. As baseline data has already been collected, please consider providing sociodemographic and behavioral characteristics of the study populations in each country. It would be helpful to provide evidence that the dietary sources of sodium are similar in these two populations, as well as the proportion of sodium intake that is derived from cooking/at the table vs from processed foods. Do you anticipate any spillover effects of sodium reduction in processed foods because many food manufacturers are transnational? Are there any voluntary efforts under way in Ghana that might limit the validity of this population as a control group? Minor Comments: Page 10, Line 17: Is this supposed to be 3.5 g/day?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. the presentation of these 5 objectives could be improved especially in light of the stated aim of evaluating the effectiveness of the SA salt policy. To my read, objective 1 (baseline measurement) has already been completed, including urine collection, and if that is the case, it is not necessary to present this as part of the study protocol. (It would just be described in the Methods of the final

manuscript(s)). The follow-up measurement will also happen "automatically" as part of SAGE, however, since this is part of the prospective study protocol, the methods for BP, urine, etc could be presented here. The core of this project seems to be a pre- and post- assessment of population blood pressure and the independent association of this with reduced sodium intake (estimated by urinary excretion and self-reported intake). A crucial part of this is the comparison with Ghana, the data from which I imagine would be pooled in the final analysis (see below). As a substudy, the authors will want to do objectives #2-3, which will provide insight into mechanisms and validate the use of proxy measures (eg spot urine and self-reported salt intake). I suggest the authors re-work this paragraph to frame their objectives more clearly for the casual reader. Again, I think the authors should stress that this is a policy impact evaluation study with a nested path/biochemical substudy (objectives 2-3)

Thank you for this comment. We agree and have simplified the objectives to read:
The primary aim of this study is to evaluate the impact of the sodium legislation on population sodium intake and blood pressure. Secondary objectives are to assess: 1) the relationship between sodium and potassium levels and blood pressure pre- and post-legislation; 2) the impact of the sodium legislation on population iodine intake; and 3) the use of spot urine samples as a proxy for 24-hour urine sample collection to measure population salt excretion in a nested biochemical analysis.

2. Conceptual model for evaluation, consideration of mixed methods. I think this study, as primarily an assessment of policy effectiveness, would benefit from an additional figure and discussion of the overarching conceptual model of how that effectiveness will be demonstrated. I am thinking specifically of the approaches used in the M&E community and the methods presented, eg, in the World Bank handbook "Impact Evaluation in Practice" (Gertler et al, see especially ch 2). For instance, using an "inputs, outputs, outcomes, impact" framework as a Figure 1, the authors might outline that they are measuring changes in inputs (regulations and education) that lead to outputs (reduced bread salt and reduced discretionary salt use; also reduced urinary sodium) that lead to outcomes (reduced blood pressure) and eventually impact (incident and fatal CVD).

Thank you for this insight and reference. We agree that a conceptual model would be beneficial and have added a ‘Results chain’ model (Figure 1). We have also taken your suggestions on board regarding the specific inputs, activities, outputs and outcomes, and adding education also as an input . As reduced discretionary salt intake would require behaviour change from the target population, we considered this an outcome with the output being a change in awareness. Gertler et al. seem to suggest that outputs are goods and services produced under the control of the implementing agency (low sodium foods and increased awareness), while outcomes are derived from the use of these outputs by the beneficiaries. We have therefore categorised the following as outputs: reduced salt intake (discretionary and non-discretionary); reduced 24-hour urinary sodium excretion; reduced blood pressure; and eventually, reduced incident and fatal CVD. The model is also explained within the methods section and the assumptions and risks further explored within the discussion section of the manuscript.

3) The latter (CVD) may be difficult to incorporate because of the anticipated lag between BP change and CVD events, and the sample size may not be adequate if there is just one wave of follow-up. Perhaps the authors could advocate for more than 1 wave of follow-up to see if there are any hard CV changes? (That would increase the effective sample size for detecting CVD though it might not be part of WHO's plans.)

Thank you for this comment. We do indeed plan to follow up the cohort past 2017 and it was an oversight that the manuscript did not clearly show this. WHO is actively pursuing grants that will support a Wave 4 of data capture to be implemented after the second phase of implementation of this legislation in 2019. We have added the following text to the discussion:
WHO-SAGE is well placed to continue follow-up in the South African cohort, as it has been

operational in South Africa since 2003 with Wave 0 of data collection[29], and plans to continue data collection after Wave 3 (2017) approximately every 4 years. This provides an ideal opportunity to collect longer term data on cardiovascular and stroke mortality and morbidity in both South Africa and Ghana.

4) Another aspect of M&E is the consideration of whether mixed methods are needed. In this case, the authors might consider doing in-depth interviews with stakeholders in government and industry as well as SAGE participants to see, over time, how the policy changes are being perceived - and whether they are being rolled out at all! This would be important corroborating information for the urinary sodium and BP data analysis -- without explicitly incorporating evidence that the policy is changing practices, the bio/clinical data could be criticized as simply reflecting secular trends. (The inclusion of Ghana data would not mitigate this - you still need some evidence that the policy is actually being executed.)

Thank you for highlighting this useful approach. We have indeed conducted a focus group with stakeholders in government, NGO's, academia and independent testing laboratories. The report from this meeting will be published soon and the manuscript now includes reference to this:
Non-compliance by targeted food manufacturers or increased salt levels in non-legislated food products (by other food producers) are risks to undermining the intended outcomes. Educational activities that do not reach the intended beneficiaries are also a risk as they may fail in the message to modify discretionary salt use. Media campaigns to reduce salt can work [57], and the key again will be in documenting and monitoring their success. As a mitigation strategy for these risks, the SAGE South Africa team are working closely with stakeholders in government, academia, non-governmental organisations and research organisations who are directly involved in monitoring compliance and/or the development, delivery and evaluation of salt and blood pressure educational activities. In September 2016, stakeholders met to develop a roadmap for the South African salt reduction strategy, with action points and a report due to be published. The meeting serves as a foundation to coordinate and link efforts. The authors will continue discussions with these stakeholders and are open to any discussions that promote a thorough and valid evaluation of the effectiveness of this important health policy.

Our colleagues in government are working closely with industry to monitor compliance and to deal with challenges, for example, debates are ongoing regarding salt levels and food safety in some processed meats.
We also agree that conducting interviews or focus groups with SAGE participants would be valuable and are looking for funding opportunities and collaborators for this work. The SAGE interview (that is delivered to 42,000+ participants worldwide) has a series of basic questions on discretionary salt use. In South Africa, it would be ideal if we can explore these behaviours further using qualitative approaches.

5) Comparing countries. The objective on Ghana-South Africa comparisons is, in my view, the weakest aspect of the protocol. Care should be taken to address how this analysis will be done. There are several approaches:
a. Simple comparison of means in SA and Ghana pre- and post-policy. Easiest to understand, but does not take into account confounders.
b. Difference-in-differences analysis. This would be a multivariate linear regression on BP vs. salt excretion/intake in the pooled sample, with dummy variables for post and South Africa and an interaction term (whose coefficient would be the item of interest). Other confounders like age and sex could also be incorporated.
c. Matching. If the SA and Ghana samples were felt to be too different (demographics, disease profile, etc) to pool completely as in (b), then a subset of Ghana patients could be matched (with replacement) as controls to the SA sample. The regression model might, instead of pre- and post-

measurements, just calculate individual-level change in BP and sodium and do a (quasi) cross-sectional analysis of this variable. This method would be inferior to (b) but may be more feasible.
If the authors do not feel comfortable carrying out this analysis themselves, I think it would be helpful to recruit a statistician or economist on the team who has experience in quantitative impact evaluation.

Thank you for your expertise and for offering these suggestions. We agree that a statistical analysis plan with input from appropriately trained statisticians will be critical. This will take the form of an evolving and separate document to the manuscript for the study protocol.

Reviewer 2
Minor revisions are needed to better justify the comparison to Ghana and explain the post-legislation measures. With revisions, this paper has great potential to provide valuable documentation describing much-needed evaluation of legislative approaches for population sodium reduction.

1) Introduction: Page 4, Lines 26-37: It would be helpful to provide more details about the legislation in South Africa, such as what foods have mandatory sodium targets (consider moving this from the Discussion to the Introduction). It would also be helpful to mention how much salt intake comes from processed food and from salt added during food preparation or at the table in South Africa.

Thank you, we agree and the following text has been moved to the introduction to read:
In South Africa, non-discretionary salt intake (salt already in processed foods) is estimated to contribute around 60% of the overall daily salt intake, primarily from bread and meat products.[6] As a result of this research, South Africa was the first country to legislate for mandatory reformulation of a range of foods in March 2013,[7] setting maximum sodium levels (mg per 100g) in targeted processed foods (bread 400mg; breakfast cereal 500mg; butter and margarine 550mg; potato crisps 650mg; salty snacks 800mg; raw sausage 800mg; processed meat 850-950mg; instant noodle mix 1500mg; dry soup powder 5,500mg; and stock concentrate 18,000mg), all identified as contributing significantly to the sodium intake of the South African population.[6 8 9] This was implemented in June 2016, with further reductions required in sodium levels across food categories by June 2019.[10]

2) Pages 4 Line 59 – Page 5 Lines 1-4: Are there other efforts to evaluate the impact of the sodium legislation in South Africa?

As far as we are aware, this is the only coordinated effort. Following comments from Reviewer 1, and our latest progress this month, the article now describes a recent stakeholder meeting that we organised with funding from WHO in collaboration with the Heart and Stroke Foundation of South Africa. From this meeting, it became clear that there are small activities being conducted in the country that can inform on parts of the policy implementation and evaluation. The meeting serves as a foundation to coordinate and link these efforts. The authors will continue discussions with these stakeholders and are open to any discussions that promote a thorough and valid evaluation of the effectiveness of this important health policy, (see also response to Reviewer 1, comment 4):

3) Methods: Page 5, Lines 50-52: Please clarify the timing of the different waves of data collection, and specify which waves will be used in the sodium evaluation. Could you also add here information about how many waves are planned in the future?

Thank you for this comment, the following information has been added (see also Reviewer 1, comment 3):
Further details about WHO-SAGE can be found via the WHO website (http://www.who.int/healthinfo/sage/cohorts/en/) including access to data from SAGE Wave 0 (2002–2004), SAGE Wave 1 (2007–2010), and SAGE Wave 2 (2014/15) following the completion of data

cleaning. SAGE Wave 3 will be implemented in 2017, with fund-raising for SAGE Wave 4 and beyond ongoing.

4) Page 5, Lines 52-57: How many respondents were included in Ghana, and what was their age distribution?

Thank you for showing this section is unclear. The methods section has now been amended to read:
Selection and data collection in the nested cohort
Both South Africa and Ghana include between 3500 to 4500 households for SAGE's main survey sample. The sample selected for urine collection (n=1200 in each country) from Waves 2 and 3 of the main study are adults aged 18-plus years, with the final distribution in both the main and nested studies reflecting the weighting toward recruiting more adults aged 50-plus years. In South Africa, the nested study respondents were sampled from among the first Wave 2 households visited within each probability sampled EA (day 1 in the EA). This approach was taken to prioritise the shipment of all collected urine samples to a central laboratory (Global Clinical and Viral Laboratory, Durban) within three days of collection whilst maintaining a cold chain regardless of where urine collection took place. This was necessary as there were no decentralised facilities available to freeze urine. The SAGE South Africa team used 20 survey teams (one nurse and three interviewers per team) simultaneously collecting data and urine/blood samples from respondents across all provinces in the country over a five-month period (August to December 2015).
Selection of the nested study sample in Ghana differed slightly from South Africa. All urine samples were collected by just four fieldwork teams (one research assistant and four interviewers per team) moving region to region over a 10-month period (September 2014 to June 2015). To facilitate this approach, EAs were randomly selected, with stratification by urban/rural, from the three geographical areas (savannah, forest and coastal) of Ghana and designated 'urine EAs' from which the target 1200 respondents were recruited.
[...] All respondents who provided samples in Wave 2 will be approached again in Wave 3 in both countries, with procedures as described earlier for replacement and refreshment of the sample.

5) Page 6, Lines 8 -20: Consider moving these sentences about the categories of households to the end of the paragraph. Clarify why the sampling strategy accounted for attrition, if all wave 1 households were included in wave 2; was there attrition?

Thank you, we have tried to clarify this by amending the text to read:
The Wave 2 sampling strategy was designed to account for expected attrition as a result of participants having moved house or died since Wave 1, especially given that over half of the sample were already above 60 years of age in 2007. All Wave 1 households were visited for Wave 2 data collection (including a verbal autopsy for those participants no longer alive). Replacements for sample attrition used a systematic sampling approach to randomly select new households using EA aerial photographic maps on which dwellings are clearly visible, starting at a random point on the periphery of the EA and following pre-determined routes. Households were then classified into the following mutually exclusive categories: 1) SAGE Wave 1 follow-up households with one or more members aged 50 years or older targeted for selection; 2) new households with one or more members aged 50 years or older; 3) SAGE Wave 1 follow-up households which include residents aged 18-49 targeted for selection; or, 4) new households which include residents aged 18-49. Younger adults are allowed to "age-in" to the older adult group, with targeted refreshing of the youngest ages (18-23) in the younger adult sample.

6) Page 6, Lines 46-52: Please provide more details about how the subsample of households was selected to provide urine samples.
Please refer to your comment 4.

7) Page 6, Lines 55-59: Provide more explanation about why the years of data collection were not the same and did not even overlap for South Africa and Ghana. Please note in the discussion whether this might have an impact of the comparison of sodium changes in these 2 countries.

Thank you, the following text has been added to the limitations of the study in the discussion:
While standard training and interview techniques, as well as survey instruments were used, there was a difference of several months in the timeframe for Wave 2 data collections in South Africa and Ghana. It is unclear if this will impact the validity of comparisons.

8) Page 7, Lines 1-3: How was the subsample selected?
Please refer to your comment 4.

9) Page 8, Lines 35-37: Is this the primary reason for not using PABA because of the participants' age range, or is it also because of the reasons mentioned in the WHO/PAHO guidelines about compliance or testing?

Thank you for this question, the text has been amended to read:
PABA recovery rate declines with age in respondents older than 30 years.[35] Considering this together with the increased risk for non-compliance and attrition due the additional burden of remembering to take the PABA pill three days before the urine collection, as discussed in the WHO/PAHO guidelines for sodium determination in 24-hour urine samples,[31] PABA is not used in this study.

10) Page 10, Line 5: What data will be collected in wave 3 (and beyond) to assess sodium or blood pressure post-legislation?

Thank you for this question. The following text has been added to the discussion to clarify this:
WHO-SAGE measures blood pressure in each wave of data collection and will continue to do this. While urinary sodium analysis is conducted only for Wave 2 and Wave 3 in the nested studies in South Africa and Ghana, from Wave 2 onward, questions on discretionary salt use have been added to SAGE for all respondents in each of the six countries. This will provide valuable data on self-reported discretionary salt behaviours as countries implement various strategies to reduce population salt intake.

11) Discussion: Page 12, Lines 14-22: Consider mentioning that this study cannot determine the impact of legislation on younger populations or individuals without hypertension.

Thank you for this comment. We disagree as the study is designed specifically to determine the impact of policy on salt and blood pressure of the population (we include normotensive, pre-hypertensive and hypertensive adults aged above 18 years of age, with an approximate 60% of this population above 50 years of age). We will make every effort to conduct a full follow-up of the nested cohort in Wave 3 (and beyond), and may have sufficient power to detect differences in younger compared to older adults. All final analysis will need to adjust for the presence of hypertension as we know from the recent Lancet paper (Mente et al. 2016, vol 388) that individuals with hypertension may show greater blood pressure lowering from salt reduction than non-hypertensive individuals, regardless of age.

12) Page 12, Line 42: What is meant by "economic modelling"? Please clarify.

We are grateful to the reviewers for their in-depth and extremely helpful comments. To avoid making the manuscript even longer, we have removed all reference to economic modelling, as it does not form part of the core purpose of this manuscript.

13) Page 12, Line 47-49: This paper is establishing the study protocol, so please add a more detailed examination and discussion of whether Ghana is a valid comparison population for South Africa.

Following both reviewers comments, the authors have added a section to the Methods specifically addressing this, the text reads:
Ghana as a comparison group
Gertler et al. (2011) also recommend including a comparison group. Ideally this would be a South African group matched on all characteristics and exposures but not affected by the legislation, with data collected at the same time as those who would be affected by the legislation. However, as the legislation is in force across the whole country, this is not possible. Neighbouring countries such as Lesotho, Swaziland, Botswana, etc. would also not be good candidates for a comparison group as many of the South African food manufacturers export goods to these countries under the South African Development Community (SADC) Regional Free Trade agreement (2008). South Africa is the major source of processed snack food in the SADC region,[20] providing around 80% of the processed food in Zambia, Namibia and Botswana.[21] These countries then would likely be affected by spill over of the South African sodium legislation. SADC countries form over 80% of South Africa's export market, with exports to the rest of Africa consisting mainly of vehicles and machinery.[22] As such Ghana, a non-SADC country and the only other African country to implement WHO-was selected as the comparator country. Ghana's adult population is also afflicted by a high prevalence of hypertension (up to 48% of adults generally [23] and 54% of adults 50-plus years of age), increasingly poor risk factor profiles (diet, obesity, physical activity), and poor rates of hypertension awareness and control.[3] In terms of salt intake, the Ghana Health Service has focused primarily on eradication of iodine deficiency through salt iodization and education.[24] At the same time, efforts are underway to boost the salt production industry in Ghana as a method of economic development.[25,26] Salt intakes appear comparable between Ghana and South Africa with studies suggesting both countries have intakes between 2.3 and 5.5g sodium/day (equivalent to 5.8-13.8g salt/day), and higher intakes in urban compared to rural populations.[27] While there have been some efforts to lower salt intake in community interventions [28], to date there appears little evidence to suggest that either mandatory or voluntary sodium targets exist between government and the food industry in Ghana to promote a reduction in population salt intake. However, as in South Africa, it will be critical to monitor activities in Ghana that could influence salt intake between Wave 2 and Wave 3 of data collection. There are some risks in taking this pragmatic approach, although local experts will provide ongoing and active assessments in both countries between study waves, and this study team will undertake rigorous comparisons of the nested study groups at Wave 2 and Wave 3 to determine the feasibility of this research strategy.

14) As baseline data has already been collected, please consider providing sociodemographic and behavioral characteristics of the study populations in each country.

Thank you for this suggestion. We would like to incorporate this data and agree it would provide support for comparing the two countries. However, the WHO-SAGE Wave 2 data (including the blood pressure and anthropometry data for all six countries) is still in the process of being cleaned by the WHO coordinating centre.

15) It would be helpful to provide evidence that the dietary sources of sodium are similar in these two populations, as well as the proportion of sodium intake that is derived from cooking/at the table vs from processed foods.

Thank you for this suggestion. We agree such a comparison is needed although we are unable to find data on the main contributing sources of sodium in the Ghanain diet with previous studies reporting methodological issues (see Gibson et al, 2015 Food Nutr Res). Data on discretionary and non-

discretionary salt intake in Ghana is also scant and controlled studies are needed using , for example, novel lithium tracer techniques to determine the relative contributions of these two salt sources. This is also true in South Africa where previous estimates require further validation. The data that is available comparing salt intakes has been added (see your comment 13).

16) Do you anticipate any spillover effects of sodium reduction in processed foods because many food manufacturers are transnational?

Thank you for this, it is a good question. At the recent stakeholder meeting this was discussed as many South African food manufacturers also export to Botswana and other SADC countries. We will continue to work with stakeholders and would encourage any research specifically to investigate this. Please also see your comment 13.

17) Are there any voluntary efforts under way in Ghana that might limit the validity of this population as a control group?
Please see the response to comment 13.

18) Page 10, Line 17: Is this supposed to be 3.5 g/day?

Thank you for looking at this data, sadly 35g/day is correct and we see some individuals with intakes exceeding 30 or even 40g per day. This has been corroborated in our collaborators and colleagues datasets, the most recent publication of which appears in JASH this month (Swanepoel et al. 2016) showing one third of the group with intakes exceeding 10g per day. To clarify this, the text has been amended to now read:
a population variance of up to 35g per day

We thank all reviewers and the editor again for the helpful comments and suggestions and look forward to the review of this revised manuscript.

The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. The manuscript now contains one table and one figure, the word count excluding references, abstract, figure and table is 5348. The authors have declared no conflict of interest and all authors have approved the manuscript for submission. Appropriate ethics committee approval has been obtained for the study.

VERSION 2 – REVIEW

REVIEWER	David Watkins University of Washington, Seattle, WA, USA
REVIEW RETURNED	27-Sep-2016

GENERAL COMMENTS	The authors have done an excellent job incorporating the suggested changes from both reviewers. The revised paper reads very well, and I am confident it will be an excellent study.

REVIEWER	Jennifer Poti University of North Carolina at Chapel Hill USA
REVIEW RETURNED	15-Oct-2016

GENERAL COMMENTS	Thank you for the opportunity to review a revised version of the manuscript now entitled “Leveraging ongoing research to evaluate the health impacts of South Africa’s salt reduction strategy, a prospective nested cohort within the WHO-SAGE multicountry, longitudinal study.” Thank you for your responsiveness to my feedback and detailed replies to my questions. The added details about the specifics about the sodium targets mandated by the legislation, choice of Ghana as a comparison country, sampling strategy, and the timing of data collection were informative and added clarity to the manuscript. The extra discussion about compliance and other aspects of implementation and effectiveness of the legislation was interesting. I have no further comments. I look forward to seeing the results of this study.