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# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China - Protocol of a cluster randomised controlled trial



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# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China

## Protocol of a cluster randomised controlled trial

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## ABSTRACT

**Introduction:** Salt intake is very high in China, with ≈80% being added by the consumers. It is difficult to reduce salt in such settings. Our previous study (School-EduSalt, School based Education programme to reduce Salt) demonstrated that educating schoolchildren who then instructed their families to reduce the amount of salt used at home, is effective in lowering salt intake in both children and adults. Our team also developed an app called "KnowSalt" which could help individuals to estimate their salt intake and the major sources of salt in the diet. Building upon School-EduSalt and KnowSalt, we propose to develop a new app (AppSalt) focusing on salt reduction through education, target setting, monitoring, evaluation, decision support and management, to achieve a progressive lower salt intake for long term. To evaluate the effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial.

**Methods and analysis:** We will recruit 54 primary schools from urban and rural areas of 3 provinces in China. 540 children aged ≈8 years and 1080 adult family members will be randomly selected for evaluation. After baseline assessment, schools will be randomly allocated to either the intervention or control group. Children in the intervention group will be taught, with support of AppSalt, about salt reduction and assigned homework to get the whole family involved in the activities to reduce salt consumption. The duration of the intervention is two school terms (i.e. 1 year). The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-h urinary sodium.

**Ethics and dissemination:** The study has been approved by Queen Mary Research Ethics Committee and Peking University Health Science Centre IRB. Results will be disseminated through presentations, publications and social media.

**Trial Registration:** Registered on Chinese Clinical Trial Registry, ChiCTR1800017553.

**Strengths and limitations of this study**

- Our study will develop a new approach to reducing salt intake, i.e. by the use of an innovative smartphone application through estimation of salt intake, education, target setting and monitoring, decision support and management, to achieve a sustainable progressive lower salt intake for long term.
- The study covers a wide range of the population including children and adults in diverse settings, e.g. rural and urban, north, central and south China, the results should be generally applicable to the whole Chinese population.
- The study will be carried out in China only. However, the method could be adapted by many other developing countries where most of the salt in the diet is added by the consumers.

## INTRODUCTION

Cardiovascular disease (CVD, i.e. strokes, heart attacks and heart failure) is the leading cause of death and disability worldwide. Approximately 80% of CVD deaths occur in developing countries.[1] Blood pressure (BP) throughout its range starting at 115/75 mmHg, is an important risk factor for CVD, accounting for 62% of strokes and 49% of coronary heart disease.[2] High salt intake is the major cause of raised BP,[3] responsible for about half of the disease burden attributable to BP. Randomised trials have demonstrated that a reduction in salt intake lowers BP in both hypertensive and normotensive individuals, in both adults and children.[4,5,6] There is also compelling evidence that a lower salt intake is associated with a reduced risk of CVD and total mortality.[7 8] Indeed, salt reduction is one of the most cost-effective measures to prevent hypertension and CVD.[3 9] The World Health Organisation (WHO) has recommended a 30% reduction in population salt intake by 2025, and also set a target of <5 g/d for all adults and lower levels for children.[10] Many developed countries have started salt reduction initiatives.[11] Salt intake has been successfully reduced in Finland and the UK, accompanied by falls in population BP and CVD mortality.[12] Developing countries, however, are lagging behind.

China is the largest developing country with one fifth of the world population. Salt intake in China is very high with an average of 12-14 g/d in adults[13-15] and 7 g/d in 10 years-old children,[13] and in some rural areas of northern China, salt intake could be as high as 18-20 g/d in adults. Approximately 80% of the salt in the Chinese diet is added by the consumers during cooking or in sauces.[16] It is extremely challenging to reduce salt intake in such settings due to the difficulty in changing individuals' dietary behaviours. Our previous study (School-EduSalt) has developed a novel and effective approach to reducing salt intake in northern China.[13] In School-EduSalt, primary schoolchildren aged ≈10 years were educated about the harmful effects of salt on health and how to reduce intake during the school's usual

health education lessons. Children then instructed their whole family to reduce salt. The results showed that, over one school term (≈3.5 months), salt intake was reduced by ≈25% in both children and adults as measured by 24h urinary sodium excretion. The reduction in salt intake led to a significant fall in systolic BP of 2.3 mmHg in adults.[13] It was estimated that, if School-EduSalt was implemented and sustained, it would prevent ≈400,000 stroke and heart attack events per year in China.

Previous studies have shown that salt reduction achieved by dietary advice attenuates over time and maintaining a lower salt intake long-term remains a challenge.[4] The School-EduSalt was successful over one school term of ≈3.5 months. The question is how to continue and reinforce the salt reduction education to achieve a sustainable, progressive lower intake to achieve the WHO's target.

Mobile technology is increasingly used in health education.[17] Recent studies have suggested that game-based intervention has great potential in changing behaviours due to the popularity of gaming.[18] China has the largest and fastest growing mobile internet population with 802 million people using internet and mobile phone penetration reached 98.3% of the population by June 2018.[19] Mobile-based decision support system has been shown to be effective in increasing medication use in individuals with high CVD risk in rural China.[20] Our team have recently developed a smartphone app (KnowSalt) which can be used by individuals to estimate their salt intake and the major sources of salt in the diet. The methodology underpinning KnowSalt app had been validated in a pilot study in primary schoolchildren and their families.[21]

Our proposed study building upon School-EduSalt and KnowSalt app will develop an innovative smartphone application focusing on salt reduction (AppSalt) through functional modules of education, evaluation, target setting and monitoring, decision support and management, with the aim of reinforcing School-EduSalt to achieve a progressive lower salt

intake for long term. To evaluate the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised trial.

## METHODS AND ANALYSIS

The project consists of 2 phases: (1) Developing AppSalt platform; (2) Carrying out a cluster randomised controlled trial.

### Phase 1 – Development of AppSalt platform

AppSalt platform comprises a smartphone app named AppSalt (family end) and a WeChat mini app (teacher end). The AppSalt consists of 4 core procedures (i.e. Education, Evaluation, Decision support and Reminding) and 3 supportive modules (i.e. Competition & Award, Supervision & Communication and SaltSwitch) (Figure 1).

***Core procedures***

1. "Education" is to educate the families about the harmful effects of salt on health and how to reduce salt intake. Nine lessons are developed, each starting with a 10-min lecture on salt reduction, followed by a few questions to test whether the families have understood the content. At the same time, the questions and answers will re-enforce the key messages. Following each lesson, the families are required to complete a practical session which is designed to help the families to prepare foods with reduced salt at home and to choose lower-salt foods when shopping.

2. "Evaluation" is to estimate salt intake and the main sources of salt for every member of the family. After completing a simple questionnaire, the family will be provided with the information on the top 3 contributors of salt in their diet. This will help the family make a decision on how to effectively reduce salt intake.

3. "Decision Support" will set target for total salt intake and specific targets for top 3 contributors. Lower-salt sample recipes and specific measures, e.g. reducing the amount of

salt used during cooking by 50%, will be recommended. The recommended measures will be customised as an action plan.

4. "Reminding" will remind the family how far their salt intakes are away from the targets set and highlight further action plans.

***Supportive modules***

1. The "Competition & Award" module will help the participants to find out their own ranking position assessed by salt intake level and extent of salt reduction among all participants (NB: only their own ranking will be displayed and other participants' ranking will not be revealed to them). The family with lowest salt intake and the family who achieve the greatest reduction in salt intake, will be the winners of competition. They will be awarded an honorary title like "Salt Reduction Pacesetter" and get a small gift.

2. The "Supervision & Communication" module will be the place to exchange experience and knowledge among the participants. The teachers will use this function to announce instructions, newsletters, and school canteen menus, as well as providing answers to any queries.

3. The "SaltSwitch" module will help the participants to choose pre-packaged foods with lower salt. "SaltSwitch", as a sub-function of "FoodSwitch"[22] integrated into the AppSalt, has a database of over 50,000 pre-packaged food collected by the George Institute China. By scanning the barcode of the pre-packaged foods, the "SaltSwitch" will provide information on salt/sodium content and compare it with other similar products based on products' labelling. This will help the participants to choose food with lower salt.

AppSalt will be installed in the smartphone of adult family members. Children are only allowed to use AppSalt accompanied by their adult family members to complete AppSalt core procedures as required. New features with a variety of presentation styles on salt reduction education will be added to keep the programme attractive to the participants.

The school teachers will use the WeChat mini app (teacher end) to send messages to the families, provide timely feedback to any queries, and check families' progress and ensure all families complete the procedures in time. The teachers will also report any issues to the site managers and the research team where appropriate.

## Phase 2 – Cluster randomised controlled trial (RCT)

To test the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial (Figure 2).

***Study Setting and participants***

Considering the geographical location, economic level and dietary habit, our study will be undertaken in selected primary schools from urban and rural areas of 3 provinces in northern (Hebei), central (Sichuan) and southern (Hunan) China.

To recruit schools, we will firstly contact the local education authority through local health Bureau or Centre for Disease Control (CDC) to gain their opinion, support and approval. We will then contact schools' head teachers to request their participation in the study. In each school, there are 6 grades with age ranging from 7 to 12 years and our study will be carried out in grade 3 (age ≈8 years). Head-teacher will choose one class whose teacher in charge is willing to collaborate with the researchers. From each class, we will randomly select 10 children and 20 adult family members (i.e. 1 child and 2 adults per family) for evaluation. The inclusion criteria are (1) Children and their adult family members have to eat homemade meals at least four times per week; (2) One of the adults in the family has a mobile device with access to Internet; (3) If more than 2 adults in one family agree to take part in the evaluation, we will select two in the order of grandparents, parents, uncles and aunties; (4) Participants have been local residents for over 6 months, without moving plan within 24 months. We will exclude the individuals who cannot or refuse to collect 24-hour urine.

***Randomisation***

Schools (clusters) will be randomly assigned (1:1) to either the intervention or the control group. Randomisation will be stratified by the location of schools (i.e. south or north, urban or rural) and the size of the class. The randomisation will be carried out using computer generated random number by an independent statistician who is blind to the identity of the schools. The randomisation will take place after the completion of baseline assessments. Therefore, the participants, school-teachers and local investigators who undertake recruitment and data collection, will be unaware of the allocation until the point prior to the commencement of the intervention.

***Intervention***

Our goal is to lower salt intake (measured by 24h urinary sodium) by a minimum of 15% (≈1.5g salt) for both children and their families. To achieve this goal, a strategy towards a 50% reduction should be implemented. To make the decision-support algorithm simple in the AppSalt, we will set targets for the top 3 contributors to salt intake, such as cooking salt, soy sauce, pickles. Targets and priority actions will be individualised depending on the sources of salt in the individual's diet which will be provided by AppSalt.

In the intervention group, the AppSalt intervention package will be delivered to all children and their families in the whole class, despite only 10 children and their families being randomly selected for evaluation. Children's adult family members will be authorized to install and operate the AppSalt programme, while children will be assigned homework to get the whole family to reduce salt with the support of AppSalt. Children's homework will include: (a) helping the family to set salt reduction target and reminding the whole family of this target on a regular basis; (b) getting the whole family involved in salt reduction activities and persuading the person who does the cooking to reduce the amount of salt used during food preparations at home; (c) working with their family members to complete the AppSalt core procedures, including education, evaluation, target setting and monitoring. In addition to

the online lessons, school teachers will organise three face-to-face seminars for both children and adults during the one-year intervention period. This will provide an opportunity for the participants to share experiences and discuss challenges and solutions. These seminars will be integrated into the schools' routine parent meetings.

Trained teachers will provide guidance on AppSalt utilisation, assign and check children's homework including monitoring the progress of salt reduction. They will also create salt-reduction environment, e.g. putting up posters in classroom, campus and canteens. The AppSalt will be activated at the beginning of the intervention for all families in the intervention group. Throughout the study, participants will receive salt reduction messages and newsletters via AppSalt on a monthly basis. Participants will be encouraged to use AppSalt and communicate with the teachers and other families to share experiences. The mandatory tasks for the participants include completing the online lessons and the related Q&As (Questions and Answers) at baseline and every month thereafter, and completing the core procedures, i.e. salt intake estimation, target setting at baseline and every 3 months thereafter. In addition to the mandatory tasks, the participants are encouraged to repeat the core procedures as often as they wish, in order to monitor their progress and achieve progressive reductions in salt intake. Based on the progress monitored from the WeChat mini app, the teachers will remind children that they should complete their homework which is to help the family complete the AppSalt procedures in time and to instruct the family members to reduce salt to the target.

The records from AppSalt, e.g. salt intake and how far the intake is different from the target set, will be used to monitor compliance. During follow-up, the participant who fails to achieve the salt reduction target, will be sent a specially designed message via AppSalt and a letter to the child through his/her teacher to remind the family of the salt reduction target.

The intervention duration is 2 school terms, i.e. 1 year. After the trial is completed, we will introduce the AppSalt to all schoolchildren including those in the control group.

***Sample size calculation***

Based on the School-EduSalt trial,[13] assuming a standard deviation of 24-hour sodium excretion is 85mmol/day, and intraclass correlation coefficient (ICC) is 0.05, we estimate that a sample size of 540 children from 54 schools (18 primary schools from each province in both urban and rural area, and 10 children per school) would provide a power of 80% (with a two-sided alpha=0.05) to detect a difference in mean 24-hour urinary sodium ≥28mmol/day (1.5 g/d salt) between intervention and control group, allowing for a 20% drop-out rate of participants. We aim to recruit 2 adults per family, therefore 1080 adults will be recruited into the study for evaluation.

***Outcome measures***

The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-hour urinary sodium from baseline to the end of the trial. The secondary outcome is the difference between the two groups in the change of systolic BP for adults.

***Outcome assessments***

All outcome measurements and assessments will be carried out at baseline and at the end of the trial in exactly the same way in all schools for all participants, irrespective of their assignment to intervention or control group.

We will carry out two consecutive 24-hour urine collections using the stringent protocol which we developed in the School-EduSalt study.[13] The participants will be carefully instructed on how to accurately collect 24h urine by trained research staff. On the first day, the participants will be asked to come to the schools. The researchers will ask the participants to empty bladder and discard the urine. The researchers will record the start time and date of

the 24h urine collection. They will then give the participants the collection equipment including containers and collection aids such as carrier bags. The participants will be instructed to collect all subsequent urine voids over the next 24h period. On the second day at the same time, the participants will be asked to bring the urine collection bottles back to the schools and they will be asked to pass the last urine into the container. The researchers will record the finish time of the first 24h urine collection. The researchers will then give the participants the collection equipment for the second 24h urine collection and repeat the process. During the 24h urine collection period, the participants will be asked to take spare urine containers with them when they go to school or work. Spare collection equipment will also be available in the schools, in case children forget to bring them. In the case that the participant misses one or more urine voids or spillage occurs, the participant will be asked to do a further 24-hour urine collection. The 24-hour urine collections will be made either at weekdays or at weekends. For each participant, the 24-hour urines will be collected on the same days of the week for baseline and for follow-up at the end of the trial.

We will measure urine volume, sodium, potassium and creatinine. Ion-selective electrode method will be used for sodium and potassium analysis and enzymatic method for creatinine assay. 24-hour urinary creatinine together with urine volume will be used to determine if the collection is likely to be complete. The biochemist who performs the measurements of urinary electrolytes will not be told which group the participant is allocated.

In addition to 24-hour urine collection, we will measure BP and heart rate using a validated automatic machine with the appropriate size of cuff. Three readings will be taken in the right arm at 1-2-minute intervals at sitting position after the participant has had 10 minutes' rest in a quiet room. Body weight, height and waist circumference will also be measured. Survey on Knowledge, Attitude and Practice (KAP) related to salt will be completed via questionnaire.

## Data collection, management and analysis

### *Data collection*

Our study will have two major data outputs. One is the "App Data" generated automatically when the AppSalt platform is used by the families in intervention group to support salt reduction. The App Data include information on demographic characteristics, eating habits, amount and sources of salt in the diet, as well as information (or App logs) on the use of AppSalt. The other data output is the "RCT Data" which is generated by both intervention and control groups during the RCT. The RCT Data will be collected through a specially designed mobile device based electronic data capture system (mEDC) by well-trained field investigators. The mEDC has been validated and widely used in other clinical trials[23] with more advantages on process and quality control compared with traditional EDC. The RCT data include information on demographics, social-economic information, KAP, measurement of height, weight, waist circumference, BP, heart rate, 24-h urine volume and electrolytes, as well as information on costs for all the components of intervention conducted through the AppSalt programme.

### *Data management*

All cleaned and locked datasets together with the study design, questionnaire, code list and definition of database and variables will be stored with a unique ID number attached but no personal identifiers in The George Institute China (TGI), following an established standard operating procedure for data security. To guarantee the data security, the mobile app developer (i.e. the IT team at Beihang University) must follow the "Mobile Application Information Service Regulation" issued by the Cyberspace Administration of China in 2016. Although personal data are accessible to app developer, disclosure of such information is prohibited. In addition to the development and maintenance of the AppSalt and mEDC, IT

team will also provide data management service during the study to guarantee the safety, integrity and proper use of the data collected through AppSalt and mEDC.

***Statistical Analysis***

The effect of the intervention on the outcomes will be tested using linear mixed models with participants nested within family units and families nested within schools. We will include group (intervention, control), time (baseline, end of trial), and time×group interaction, with the time×group interaction term indicating differential change by group from baseline to the end of the trial. We will adjust for the stratification variables at randomization and potential confounding variables. Various sensitivity analyses will be carried out to examine the robustness of the conclusions of the primary analysis. Results will be reported as mean, SD, SE, and 95% confidence interval when appropriate. All analyses will be two sided and $P<0.05$ is considered significant. SAS will be used for the analyses.

***Economic evaluation and process evaluation***

Economic evaluations will be carried out from health sector perspective to compare the m-Health strategy with usual care and it will entail two components: a trial-based economic evaluation and a modelled economic evaluation of long-term costs and outcomes. Intervention costs will include those in running the programme but exclude any research and development costs. The trial-based economic evaluation will be assessed initially in terms of incremental cost per unit reduction in salt intake and systolic BP. The modelled economic evaluation with discounting will examine the cost, survival, quality of life over lifetime, via capturing various health states (including death and CVD events) to estimate incremental cost per life year saved and cost per Quality-Adjusted Life Year (QALY) gained. The transition probabilities across health states and costs attached to various health states will be based on literatures and the long-term effects of salt reduction or systolic BP will be derived from the

trial findings and/or literatures of disease progression. Sensitivity analyses will be carried out to estimate uncertainty about the primary findings associated with varying key parameters.

Mixed-method process evaluations will be conducted during and at the end of the study using data from AppSalt, key informant interviews with researchers and teachers, and focus groups interviews with participants. This will help understand the barriers and facilitators of the intervention as well as the acceptance and effect of the AppSalt programme.

**Project status and timelines**

Recruitment of schools and participants started in September 2018. Baseline assessments are underway with one province (Hebei) completed and the other two provinces are to complete baseline surveys by November 2018. As the intervention duration is one year, the final follow-up assessments will be carried out between September and November 2019.

**Expected outcome and potential impact**

The study will provide a novel, feasible and effective approach to achieving sustainable reduction in salt intake in both children and adults. The use of AppSalt platform in delivering health education is particularly advantageous over the traditional school education method in terms of reducing the burden on teaching staff. Furthermore, our study covers a wide range of the populations (children and adults, rural and urban, north and south), the results should therefore be generally applicable to the whole country. If the programme is implemented and sustained across China, it will reduce population salt intake and thereby prevent hundreds of thousands of strokes, heart attacks and heart failure each year, and lead to major cost-savings to individuals, their families and the health service.

Although our study will be carried out in China, the AppSalt programme could potentially be adapted by many other countries. Additionally, our model on salt reduction could possibly be adapted for other dietary and lifestyle changes to prevent CVD and other non-communicable diseases, which will have major public health implications.

## ETHICS AND DISSEMINATION

The study has been approved by Queen Mary Research Ethics Committee in the UK (QMERC2018/13) and Peking University IRB in China (IRB00001052-18051). Written consent will be obtained from all participants according to well-established practices. For children, participant assent and parental written consent will be obtained. All participants will be free to discontinue their participation at any time with no explanation required.

The findings of this study will be disseminated widely through conference presentations, peer-reviewed publications, press release and social media. Furthermore, the results will be disseminated worldwide through World Action on Salt and Health[24] which is a global non-profit organisation of 600 members from 100 countries with the mission to improve the health of populations by reducing salt intake.

**Authors' contributions:** FJH and PZ conceived the project and contribute equally to the work. FJH, PZ, YL and RL designed the study. All authors contributed to the development of the AppSalt intervention and evaluation. FH wrote the first draft of the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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**Competing interests**: FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH and Chairman of WASH. BPUK, CASH and WASH are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. Other authors declare no competing interests.

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# Figure Legends

**Figure 1.** AppSalt core procedures and modules.

**Figure 2.** Appsalt trial design. BP: Blood Pressure.

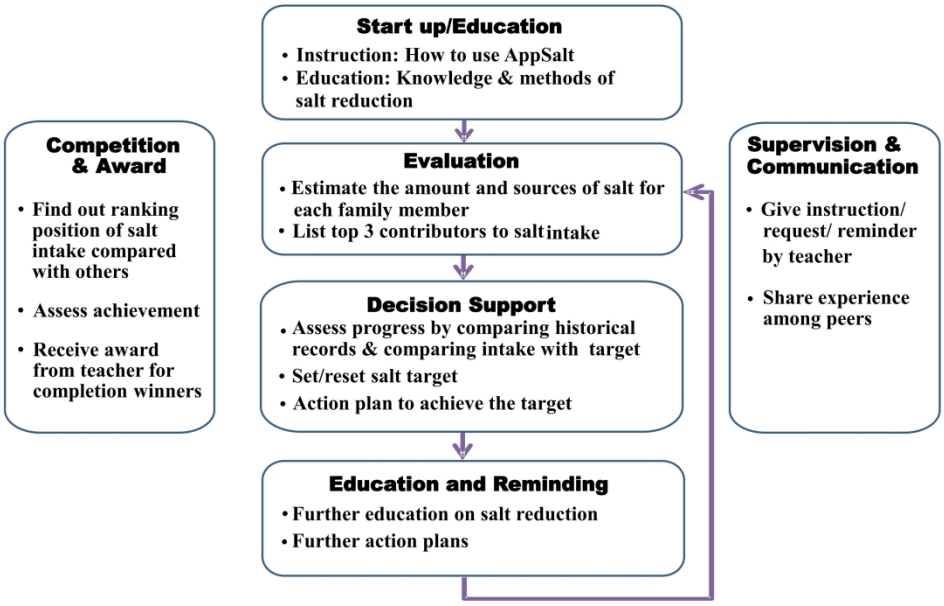


Figure 1 AppSalt core procedures and modules.

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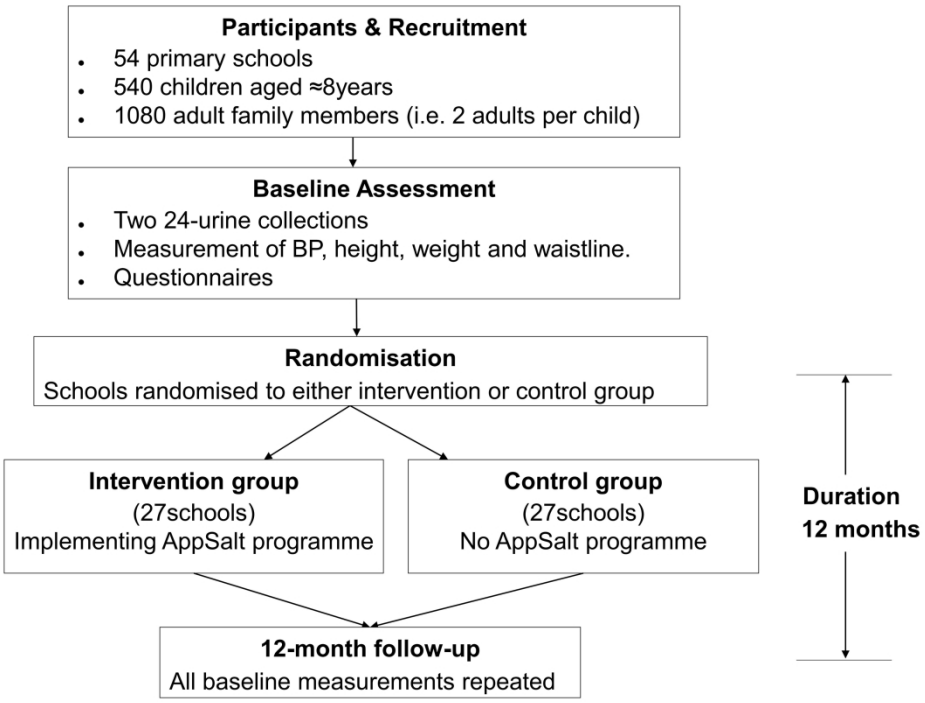


Figure 2 Appsalt trial design. BP: Blood Pressure.

266x190mm (300 x 300 DPI)

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-5 |
| | 2b | Specific objectives or hypotheses | 5 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6-10 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 8 |
| | 4b | Settings and locations where the data were collected | 8 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-10 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 11 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 12 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | Not applicable |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 14 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 14 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Not applicable |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | Not applicable |
| | 14b | Why the trial ended or was stopped | Not applicable |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Not applicable |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Not applicable |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Not applicable |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | Not applicable |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Not applicable |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | Not applicable |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 3 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 15 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 15 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 2 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Reference 24 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 16 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.









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# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China - Protocol of a cluster randomised controlled trial



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| | |

# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China

## Protocol of a cluster randomised controlled trial

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## ABSTRACT

**Introduction:** Salt intake is very high in China, with ≈80% being added by the consumers. It is difficult to reduce salt in such settings. Our previous study (School-EduSalt, School based Education programme to reduce Salt) demonstrated that educating schoolchildren who then instructed their families to reduce the amount of salt used at home, is effective in lowering salt intake in both children and adults. Our team also developed an app called "KnowSalt" which could help individuals to estimate their salt intake and the major sources of salt in the diet. Building upon School-EduSalt and KnowSalt, we propose to develop a new app (AppSalt) focusing on salt reduction through education, target setting, monitoring, evaluation, decision support and management, to achieve a progressive lower salt intake for long term. To evaluate the effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial.

**Methods and analysis:** We will recruit 54 primary schools from urban and rural areas of 3 provinces in China. 594 children aged ≈8 years and 1188 adult family members will be randomly selected for evaluation. After baseline assessment, schools will be randomly allocated to either the intervention or control group. Children in the intervention group will be taught, with support of AppSalt, about salt reduction and assigned homework to get the whole family involved in the activities to reduce salt consumption. The duration of the intervention is two school terms (i.e. 1 year). The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-hour urinary sodium.

**Ethics and dissemination:** The study has been approved by Queen Mary Research Ethics Committee and Peking University Health Science Centre IRB. Results will be disseminated through presentations, publications and social media.

**Trial Registration:** Registered on Chinese Clinical Trial Registry, ChiCTR1800017553.

**Strengths and limitations of this study**

- Our study will develop a new approach to achieving a sustainable progressive lower salt intake for long term.
- The study will use an innovative smartphone application through estimation of salt intake, education, target setting and monitoring, decision support and management to implement a salt reduction programme.
- The study covers a wide range of the population including children and adults in diverse settings, e.g. rural and urban, north, central and south China.
- The results should be generally applicable to the whole Chinese population.
- The study will be carried out in China only, however, the method could potentially be adapted by many other developing countries where most of the salt in the diet is added by the consumers.

## INTRODUCTION

Cardiovascular disease (CVD, i.e. strokes, heart attacks and heart failure) is the leading cause of death and disability worldwide. Approximately 80% of CVD deaths occur in developing countries.[1] Raised blood pressure (BP) is an important risk factor for CVD, accounting for 62% of strokes and 49% of coronary heart disease.[2] High salt intake is the major cause of raised BP.[3] Randomised trials have demonstrated that a reduction in salt intake lowers BP in both hypertensive and normotensive individuals, in both adults and children.[4,5,6] There is also compelling evidence that a lower salt intake is associated with a reduced risk of CVD and total mortality.[7 8] Indeed, salt reduction is one of the most cost-effective measures to prevent hypertension and CVD.[3 9] The World Health Organisation (WHO) has recommended a 30% reduction in population salt intake by 2025, and also set a target of <5 g/d for all adults and lower levels for children.[10] Many developed countries have started salt reduction initiatives.[11] Salt intake has been successfully reduced in Finland and the UK, accompanied by falls in population BP and CVD mortality.[12] Developing countries, however, are lagging behind. China is the largest developing country with one fifth of the world population. Salt intake in China is very high with an average of 12-14 g/d in adults[13-15], and in some rural areas of northern China, salt intake could be as high as 18-20 g/d.[16] Approximately 80% of the salt in the Chinese diet is added by the consumers during cooking or in sauces.[17] It is extremely challenging to reduce salt intake in such settings due to the difficulty in changing individuals' dietary behaviours. Our previous study (School-EduSalt) has developed a novel and effective approach to reducing salt intake in northern China.[13] In School-EduSalt, primary schoolchildren aged ≈10 years were educated about the harmful effects of salt on health and how to reduce intake during the school's usual health education lessons. Children then instructed their families to reduce salt. The results showed that, over one school term (≈3.5 months), salt intake was reduced by ≈25% in both children and adults as measured by 24-

hour urinary sodium excretion. The reduction in salt intake led to a significant fall in systolic BP of 2.3 mmHg in adults.[13] It was estimated that, if School-EduSalt was implemented and sustained, it would prevent ≈400,000 stroke and heart attack events per year in China.

Previous studies have shown that salt reduction achieved by dietary advice attenuates over time and maintaining a lower salt intake long-term remains a challenge.[4] The School-EduSalt was successful over one school term of ≈3.5 months. The question is how to continue and reinforce the salt reduction education to achieve a sustainable, progressive lower intake to achieve the WHO's target.

Mobile technology is increasingly used in health education.[18] Recent studies have suggested that game-based intervention has great potential in changing behaviours due to the popularity of gaming.[19] China has the largest and fastest growing mobile internet population with 802 million people using internet and mobile phone penetration reached 98.3% of the population by June 2018.[20] Mobile-based decision support system has been shown to be effective in increasing medication use in individuals with high CVD risk in rural China.[21] Our team have recently developed a smartphone app (KnowSalt) which can be used by individuals to estimate their salt intake and the major sources of salt in the diet. The methodology underpinning KnowSalt app had been validated in a pilot study in primary schoolchildren and their families.[22]

Our proposed study building upon School-EduSalt and KnowSalt app will develop an innovative smartphone application focusing on salt reduction (AppSalt) through functional modules of education, evaluation, target setting and monitoring, decision support and management, with the aim of reinforcing School-EduSalt to achieve a progressive lower salt intake for long term. To evaluate the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised trial.

## METHODS AND ANALYSIS

The project consists of 2 phases: (1) Developing AppSalt platform; (2) Carrying out a cluster randomised controlled trial.

## Phase 1 – Development of AppSalt platform

AppSalt platform comprises a smartphone app named AppSalt (family end) and a WeChat mini app (teacher end). The AppSalt consists of 4 core procedures (i.e. Education, Evaluation, Decision support and Reminding) and 3 supportive modules (i.e. Competition & Award, Supervision & Communication and SaltSwitch) (Figure 1).

***Core procedures***

1. "Education" is to educate the families about the harmful effects of salt on health and how to reduce salt intake. Nine lessons are developed, each starting with a 10-min lecture on salt reduction, followed by a few questions to test whether the families have understood the content. At the same time, the questions and answers will re-enforce the key messages. Following each lesson, the families are required to complete a practical session which is designed to help the families to prepare foods with reduced salt at home and to choose lower-salt foods when shopping.

2. "Evaluation" is to estimate salt intake and the main sources of salt for every member of the family. After completing a simple questionnaire, the family will be provided with the information on the top 3 contributors of salt in their diet. This will help the family make a decision on how to effectively reduce salt intake.

3. "Decision Support" will set target for total salt intake and specific targets for top 3 contributors. Lower-salt sample recipes and specific measures, e.g. reducing the amount of salt used during cooking by 50%, will be recommended. The recommended measures will be customised as an action plan.

4. "Reminding" will remind the family how far their salt intakes are away from the targets set and highlight further action plans.

***Supportive modules***

1. The "Competition & Award" module will help the participants to find out their own ranking position assessed by salt intake level and the extent of salt reduction among all participants (NB: only their own ranking will be displayed and other participants' ranking will not be revealed to them). The family with lowest salt intake and the family who achieve the greatest reduction in salt intake, will be the winners of competition. They will be awarded an honorary title like "Salt Reduction Pacesetter" and get a small gift.

2. "Supervision & Communication" module: The teachers and researchers will use the function "Supervision" to announce instructions, newsletters, and school canteen menus, as well as to provide answers to any queries. The participants will use the function "Communication" to ask any questions and also to exchange experience and knowledge with other participants.

3. The "SaltSwitch" module will help the participants to choose pre-packaged foods with lower salt. "SaltSwitch", as a sub-function of "FoodSwitch"[23] integrated into the AppSalt, has a database of over 50,000 pre-packaged food collected by the George Institute China. By scanning the barcode of the pre-packaged foods, the "SaltSwitch" will provide information on salt/sodium content and compare it with other similar products based on products' labelling. This will help the participants to choose food with lower salt.

AppSalt will be installed in the smartphone of adult family members. Children are only allowed to use AppSalt accompanied by their adult family members to complete AppSalt core procedures as required. New features with a variety of presentation styles on salt reduction education will be added to keep the programme attractive to the participants.

The school teachers will use the WeChat mini app (teacher end) to send messages to the families, provide timely feedback to any queries, and check families' progress and ensure all families complete the procedures in time. The teachers will also report any issues to the site managers and the research team where appropriate.

## Phase 2 ─ Cluster randomised controlled trial (RCT)

To test the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial (Figure 2).

***Study Setting and participants***

Considering the geographical location, economic level and dietary habit, our study will be undertaken in selected primary schools from urban and rural areas of 3 provinces in northern (Hebei), central (Sichuan) and southern (Hunan) China.

To recruit schools, we will firstly contact the local education authority through local Health/Education Bureau or Centre for Disease Control (CDC) to gain their opinion, support and approval. We will then contact schools' head-teachers to request their participation in the study. In each school, there are 6 grades with age ranging from 7 to 12 years and our study will be carried out in grade 3 (age ≈8 years). Head-teacher will choose one class whose teacher in charge is willing to collaborate with the researchers. From each class, we will randomly select 11 children and 22 adult family members (i.e. 1 child and 2 adults per family) for evaluation.

The inclusion criteria are (1) Children and their adult family members have to eat homemade meals at least four times per week; (2) One of the adults in the family has a mobile device with access to Internet; (3) If more than 2 adults in one family agree to take part in the evaluation, we will select two in the order of grandparents, parents, uncles and aunties; (4) Participants have been local residents for over 6 months, without moving plan within 24 months. We will exclude the individuals who cannot or refuse to collect 24-hour urine.

***Randomisation***

Schools (clusters) will be randomly assigned (1:1) to either the intervention or the control group. Randomisation will be stratified by the location of schools (i.e. south or north, urban or rural) and the size of the class. The randomisation will be carried out using computer generated random number by an independent statistician who is blind to the identity of the schools. The randomisation will take place after baseline data collection has completed. Therefore, the participants, school-teachers and local investigators who undertake recruitment and data collection, will be unaware of the allocation until the point prior to the commencement of the intervention.

***Intervention***

Our goal is to lower salt intake (measured by 24-hour urinary sodium) by a minimum of 15% (≈1.5g salt) for both children and their families. To achieve this goal, a strategy towards a 50% reduction should be implemented. To make the decision-support algorithm simple in the AppSalt, we will set targets for the top 3 contributors to salt intake, such as cooking salt, soy sauce. Targets and priority actions will be individualised depending on the sources of salt in the individual's diet which will be provided by AppSalt.

In the intervention group, the AppSalt intervention package will be delivered to all children and their families in the whole class, despite only 11 children and their families being randomly selected for evaluation. The adult family members will be authorized to install and operate the AppSalt programme, while children will be assigned homework to get the whole family to reduce salt with the support of AppSalt. Children's homework will include: (a) helping the family to set salt reduction target and reminding the whole family of this target on a regular basis; (b) getting the whole family involved in salt reduction activities and persuading the person who does the cooking to reduce the amount of salt used during food preparations at home; (c) working with their family members to complete the AppSalt core

procedures, including education, evaluation, target setting and monitoring. In addition to the online lessons, school teachers will organise three face-to-face seminars for both children and adults during the one-year intervention period. This will provide an opportunity for the participants to share experiences and discuss challenges and solutions. These seminars will be integrated into the schools' routine parent meetings.

Trained teachers will provide guidance on AppSalt utilisation, assign and check children's homework including monitoring the progress of salt reduction. They will also create salt-reduction environment, e.g. putting up posters in classroom, campus and canteens. The AppSalt will be activated at the beginning of the intervention for all families in the intervention group. Throughout the study, participants will receive salt reduction messages and newsletters via AppSalt on a monthly basis. Participants will be encouraged to use AppSalt and communicate with the teachers and other families to share experiences. The mandatory tasks for the participants include completing the online lessons and the related Q&As (Questions and Answers) at baseline and every month thereafter, and completing the core procedures, i.e. salt intake estimation, target setting at baseline and every 3 months thereafter. In addition to the mandatory tasks, the participants are encouraged to repeat the core procedures as often as they wish, in order to monitor their progress and achieve progressive reductions in salt intake. Based on the progress monitored from the WeChat mini app, the teachers will remind children that they should complete their homework which is to help the family complete the AppSalt procedures in time and to instruct the family members to reduce salt to the target.

The records from AppSalt, e.g. salt intake and how far the intake is different from the target set, will be used to monitor compliance. During follow-up, the participant who fails to achieve the salt reduction target, will be sent a specially designed message via AppSalt and a letter to the child through his/her teacher to remind the family of the salt reduction target.

The intervention duration is 2 school terms, i.e. 1 year. After the trial is completed, we will introduce the AppSalt to all schoolchildren and their families including those in the control group.

***Sample size calculation***

Based on the School-EduSalt trial,[13] assuming a standard deviation of 24-hour sodium excretion is 85mmol/day, and intraclass correlation coefficient (ICC) is 0.05, we estimate that a sample size of 594 children from 54 schools (18 primary schools from each province in both urban and rural area, and 11 children per school) would provide a power of 80% (with a two-sided alpha=0.05) to detect a difference in mean 24-hour urinary sodium ≥26mmol/day (1.5 g/d salt) between intervention and control group, allowing for a 15% drop-out rate of participants. We aim to recruit 2 adults per family, therefore 1188 adults will be recruited into the study for evaluation.

***Outcome measures***

The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-hour urinary sodium from baseline to the end of the trial. The secondary outcome is the difference between the two groups in the change of systolic BP for adults.

***Outcome assessments***

All outcome measurements and assessments will be carried out at baseline and at the end of the trial in exactly the same way in all schools for all participants, irrespective of their assignment to intervention or control group.

We will carry out two consecutive 24-hour urine collections using the stringent protocol which we developed in the School-EduSalt study.[13] The participants will be carefully instructed on how to accurately collect 24-hour urine by trained research staff. On the first day, the participants will be asked to come to the schools. The researchers will ask the

participants to empty bladder and discard the urine. The researchers will record the start time and date of the 24-hour urine collection. They will then give the participants the collection equipment including containers and collection aids such as carrier bags. The participants will be instructed to collect all subsequent urine voids over the next 24-hour period. On the second day at the same time, the participants will be asked to bring the urine collection bottles back to the schools and they will be asked to pass the last urine into the container. The researchers will record the finish time of the first 24-hour urine collection. The researchers will then give the participants the collection equipment for the second 24-hour urine collection and repeat the process. During the 24-hour urine collection period, the participants will be asked to take spare urine containers with them when they go to school or work. Spare collection equipment will also be available in the schools, in case children forget to bring them. In the case that the participant misses one or more urine voids or spillage occurs, the participant will be asked to do a further 24-hour urine collection. The 24-hour urine collections will be made either at weekdays or at weekends. For each participant, the 24-hour urines will be collected on the same days of the week for baseline and for follow-up at the end of the trial.

We will measure urine volume, sodium, potassium and creatinine. Ion-selective electrode method will be used for sodium and potassium analysis and enzymatic method for creatinine assay. 24-hour urinary creatinine together with urine volume will be used to determine if the collection is likely to be complete. The biochemist who performs the measurements of urinary electrolytes will not be told which group the participant is allocated.

In addition to 24-hour urine collection, we will measure BP and heart rate using a validated automatic machine with the appropriate size of cuff. Three readings will be taken in the right arm at 1-2-minute intervals at sitting position after the participant has had 10 minutes' rest in

a quiet room. Body weight, height and waist circumference will also be measured. Survey on Knowledge, Attitude and Practice (KAP) related to salt will be completed via questionnaire.

## Data collection, management and analysis

### *Data collection*

Our study will have two major data outputs. One is the "App Data" generated automatically when the AppSalt platform is used by the families in intervention group to support salt reduction. The App Data include information on demographic characteristics, eating habits, amount and sources of salt in the diet, as well as information (or App logs) on the use of AppSalt. The other data output is the "RCT Data" which is generated by both intervention and control groups during the RCT. The RCT Data will be collected through a specially designed mobile device based electronic data capture system (mEDC) by well-trained field investigators. The mEDC has been validated and widely used in other clinical trials[24] with more advantages on process and quality control compared with traditional EDC. The RCT data include information on demographics, social-economic information, KAP, measurement of height, weight, waist circumference, BP, heart rate, 24-hour urine volume and electrolytes, as well as information on costs for all the components of intervention conducted through the AppSalt programme.

### *Data management*

All cleaned and locked datasets together with the study design, questionnaire, code list and definition of database and variables will be stored with a unique ID number attached but no personal identifiers in The George Institute China (TGI), following an established standard operating procedure for data security. To guarantee the data security, the mobile app developer (i.e. the IT team at Beihang University) must follow the "Mobile Application Information Service Regulation" issued by the Cyberspace Administration of China in 2016.

Although personal data are accessible to app developer, disclosure of such information is prohibited. In addition to the development and maintenance of the AppSalt and mEDC, IT team will also provide data management service during the study to guarantee the safety, integrity and proper use of the data collected through AppSalt and mEDC.

***Statistical Analysis***

Data analyses will be performed according to the intention-to-treat approach. The effect of the intervention on the outcomes will be tested using linear mixed models with participants nested within family units and families nested within schools. We will include group (intervention, control), time (baseline, end of trial), and time×group interaction, with the time×group interaction term indicating differential change by group from baseline to the end of the trial. We will adjust for the stratification variables at randomization and potential confounding variables. Various sensitivity analyses will be carried out to examine the robustness of the conclusions of the primary analysis. Results will be reported as mean, SD, SE, and 95% confidence interval where appropriate. All analyses will be two sided and $P<0.05$ is considered significant. SAS will be used for the analyses.

***Economic evaluation and process evaluation***

Economic evaluations will be carried out from health sector perspective to compare the m-Health strategy with usual care and it will entail two components: a trial-based economic evaluation and a modelled economic evaluation of long-term costs and outcomes. Intervention costs will include those in running the programme but exclude any research and development costs. The trial-based economic evaluation will be assessed initially in terms of incremental cost per unit reduction in salt intake and systolic BP. The modelled economic evaluation with discounting will examine the cost, survival, quality of life over lifetime, via capturing various health states (including death and CVD events) to estimate incremental cost per life year saved and cost per Quality-Adjusted Life Year (QALY) gained. The transition

probabilities across health states and costs attached to various health states will be based on literatures and the long-term effects of the reduction in salt intake or systolic BP will be derived from the trial findings and/or literatures of disease progression. Sensitivity analyses will be carried out to estimate uncertainty about the primary findings associated with varying key parameters.

Mixed-method process evaluations will be conducted during and at the end of the study using data from AppSalt, key informant interviews with researchers and teachers, and focus groups interviews with participants. This will help understand the barriers and facilitators of the intervention as well as the acceptance and effect of the AppSalt programme.

**Project status and timelines**

Recruitment of schools and participants started in September 2018. Baseline assessments were carried out between September and December 2018. As the intervention duration is one year, the final follow-up assessments will be carried out between September and December 2019.

**Expected outcome and potential impact**

The study will provide a novel, feasible and effective approach to achieving a sustainable reduction in salt intake in both children and adults. The use of AppSalt platform in delivering health education lessons is particularly advantageous over the traditional school education method in terms of reducing the burden on teaching staff. Furthermore, our study covers a wide range of the population (children and adults, rural and urban, north and south), the results should therefore be generally applicable to the whole Chinese population. If the programme is implemented and sustained across China, it will reduce population salt intake and thereby prevent hundreds of thousands of strokes, heart attacks and heart failure each year, and lead to major cost-savings to individuals, their families and the health service.

Although our study will be carried out in China, the AppSalt programme could potentially be adapted by many other countries. Additionally, our model on salt reduction could possibly be adapted for other dietary and lifestyle changes to prevent CVD and other non-communicable diseases, which will have major public health implications.

## Patient and Public Involvement

During the development of the study protocol, we had 2 round-table meetings with 6 head-teachers from 3 different cities and numerous telephone meetings with teachers and children's parents to gain their opinion, particularly on the feasibility of carrying out the study in school settings and how to incorporate the intervention programme into the school curriculum. During the study, school teachers will assign and check children's homework. Both teachers and head-teachers will be informed of the study progress by monthly communication via newsletters, WeChat and website. Upon completion of the study, we will disseminate the results to head-teachers, teachers, children and their parents. We will also discuss with them and other stakeholders on how to transfer research findings into practice.

## ETHICS AND DISSEMINATION

The study has been approved by Queen Mary Research Ethics Committee in the UK (QMERC2018/13) and Peking University IRB in China (IRB00001052-18051). Written consent will be obtained from all participants according to well-established practices. For children, participant assent and parental written consent will be obtained. All participants will be free to discontinue their participation at any time with no explanation required.

The findings of this study will be disseminated widely through conference presentations, peer-reviewed publications, press release and social media. Furthermore, the results will be disseminated worldwide through World Action on Salt and Health[25] which is a global non-profit organisation of 600 members from 100 countries with the mission to improve the health of populations by reducing salt intake.

**Authors' contributions:** FJH and PZ conceived the project and contribute equally to the work. FJH, PZ, YLi and RL designed the study and oversaw the conceptualisation and development of the app. PZ, YLi, RL, FC, YZ, WZ, DL, HC, TW, JY, JL and SZ facilitates Patient and Public Involvement and were responsible for setting up the study in each site. YLiu and RL are leading the development and maintenance of the app. XL and CW contributed to sample size calculation and analysis plan. All authors contributed to the development of the intervention and evaluation. FJH wrote the first draft of the manuscript, and PZ, YLi, RL, CW and GAM revised the draft. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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**Competing interests**: FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH and Chairman of WASH. BPUK, CASH and WASH are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. Other authors declare no competing interests.

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**Word Count**: 4008 words.

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# Figure Legends

**Figure 1.** AppSalt core procedures and modules.

**Figure 2.** Appsalt trial design. BP: Blood Pressure.

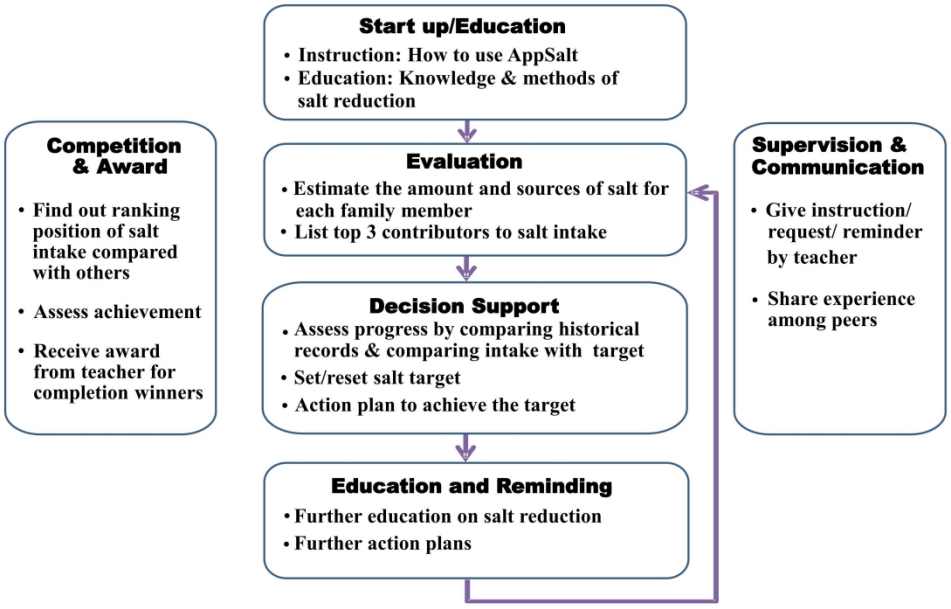


Figure 1 AppSalt core procedures and modules.

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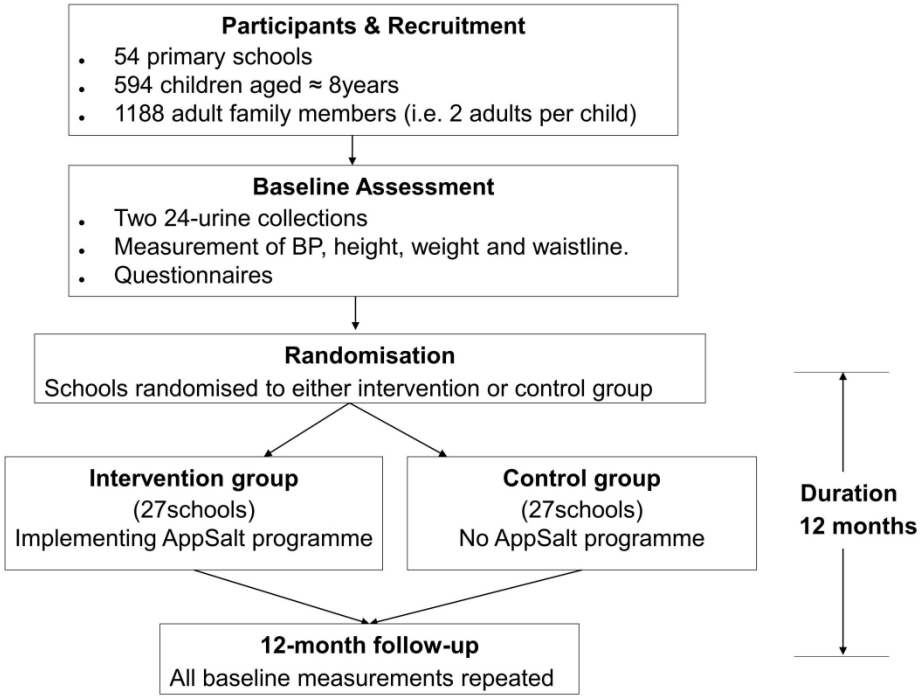


Figure 2 Appsalt trial design. BP: Blood Pressure.

267x190mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym<br>**An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China Protocol of a cluster randomised controlled trial** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br>**ChiCTR1800017553** |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br>**Yes** |
| Protocol version | 3 | Date and version identifier<br>**N/A** |
| Funding | 4 | Sources and types of financial, material, and other support<br>**Page 17** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br>**Page 17** |
| | 5b | Name and contact information for the trial sponsor<br>**Queen Mary University of London** |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities<br>**None** |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)<br>**N/A** |

| | | |
|---|---|---|
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Page 4-5** |
| | 6b | Explanation for choice of comparators **Page 11-12** |
| Objectives | 7 | Specific objectives or hypotheses **Page 9** |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page 8-10** |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Page 8** |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Page 8** |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Page 9-10** |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **N/A** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Page 10** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial **N/A** |

| | | |
|---|---|---|
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended<br>**Page 11-12** |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)<br>**Page 15** |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations<br>**Page 11** |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size<br>**Page 8** |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions<br>**Page 8-9** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned<br>**Page 8-9** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br>**Page 9** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br>**Page 12** |

| | | |
|---|---|---|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br>**N/A** |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol<br>**Page 13** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols<br>**Page 7-8** |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol<br>**Page 13-14** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol<br>**Page 14** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br>**Page 14** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)<br>**Page 14** |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed<br>**N/A** |

| | | |
|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial<br>**N/A** |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct<br>**N/A** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br>**N/A** |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br>**Page 16** |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)<br>**Page 16** |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br>**Page 16** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br>**N/A** |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial<br>**Page 13-14** |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br>**Page 17** |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators<br>**Page 13-14** |

| | | |
|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation<br>**N/A** |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions<br>**Page 16** |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br>**N/A** |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br>**N/A** |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br>**Available Upon Request** |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable<br>**N/A** |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-5 |
| | 2b | Specific objectives or hypotheses | 5 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6-10 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 8 |
| | 4b | Settings and locations where the data were collected | 8 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-10 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 11 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 9 |

| | | | |
|---|---|---|---|
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 12 |
| | 11b | If relevant, description of the similarity of interventions | Not applicable |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 14 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 14 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Not applicable |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | Not applicable |
| | 14b | Why the trial ended or was stopped | Not applicable |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Not applicable |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Not applicable |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Not applicable |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | Not applicable |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Not applicable |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | Not applicable |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 3 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 15 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 15 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 2 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Not applicable |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 17 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China Protocol of a cluster randomised controlled trial

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-027793.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 28-Mar-2019 |
| Complete List of Authors: | He, Feng; Queen Mary University of London, Wolfson Institute of Preventive Medicine<br>Zhang, Puhong ; The George Institute at Peking University Health Science Center; University of New South Wales, Faculty of Medicine<br>Luo, Rong; The George Institute for Global Health at Peking University Health Science Center<br>Li, Yuan; The George Institute for Global Health, Peking University Health Science Centre; University of New South Wales, Faculty of Medicine<br>Chen, Fengge; Shijiazhuang Center for Disease Control and Prevention<br>Zhao, Yuhong; Changan Center for Disease Control and Prevention<br>Zhao, Wei; Shijiazhuang Center for Disease Control and Prevention<br>Li, Daoxi; Luzhou Center for Disease Control and Prevention<br>Chen, Hang; Luzhou Center for Disease Control and Prevention<br>Wu, Tianyong; Luzhou Center for Disease Control and Prevention<br>Yao, Jianyun; Yueyang Center for Disease Control and Prevention<br>Li, Jinbao; Yueyang Center for Disease Control and Prevention<br>Zhou, Siyuan; Yueyang Center for Disease Control and Prevention<br>Liu, Yu; Beihang University, School of Computing<br>Li , Xian; The George Institute for Global Health at Peking University Health Science Center<br>Wang, Changqiong; Queen Mary University of London, Wolfson Institute of Preventive Medicine<br>MacGregor, Graham; Queen Mary University of London, Wolfson Institute of Preventive Medicine |
| Primary Subject Heading: | Public health |
| Secondary Subject Heading: | Global health, Public health |
| Keywords: | Salt Reduction, Schoolchildren and Families, m-Health, Randomised Controlled Trial |
| | |

# An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China

## Protocol of a cluster randomised controlled trial

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## ABSTRACT

**Introduction:** Salt intake is very high in China, with ≈80% being added by the consumers. It is difficult to reduce salt in such settings. Our previous study (School-EduSalt, **School**-based **Edu**cation programme to reduce **Salt**) demonstrated that educating schoolchildren who then instructed their families to reduce the amount of salt used at home, is effective in lowering salt intake in both children and adults. Our team also developed an app called "KnowSalt" which could help individuals to estimate their salt intake and the major sources of salt in the diet. Building upon School-EduSalt and KnowSalt, we propose to develop a new app (AppSalt) focusing on salt reduction through education, target setting, monitoring, evaluation, decision support and management, to achieve a progressive lower salt intake for long term. To evaluate the effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial.

**Methods and analysis:** We will recruit 54 primary schools from urban and rural areas of 3 provinces in China. 594 children aged 8-9 years and 1188 adult family members will be randomly selected for evaluation. After baseline assessment, schools will be randomly allocated to either the intervention or control group. Children in the intervention group will be taught, with support of AppSalt, about salt reduction and assigned homework to get the whole family involved in the activities to reduce salt consumption. The duration of the intervention is two school terms (i.e. 1 year). The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-hour urinary sodium.

**Ethics and dissemination:** The study has been approved by Queen Mary Research Ethics Committee and Peking University Health Science Centre IRB. Results will be disseminated through presentations, publications and social media.

**Trial Registration:** Registered on Chinese Clinical Trial Registry, ChiCTR1800017553.

**Strengths and limitations of this study**

- Our study will develop a new approach to achieving a sustainable progressive lower salt intake for long term.
- The study will use an innovative smartphone application through estimation of salt intake, education, target setting and monitoring, decision support and management to implement a salt reduction programme.
- The study covers a wide range of the population including children and adults in diverse settings, e.g. rural and urban, northern, central and southern China.
- The results should be generally applicable to the whole Chinese population.
- The study will be carried out in China only, however, the method could potentially be adapted by many other developing countries where most of the salt in the diet is added by the consumers.

## INTRODUCTION

Cardiovascular disease (CVD, i.e. strokes, heart attacks and heart failure) is the leading cause of death and disability worldwide. Approximately 80% of CVD deaths occur in developing countries.[1] Raised blood pressure (BP) is an important risk factor for CVD, accounting for 62% of strokes and 49% of coronary heart disease.[2] High salt intake is the major cause of raised BP.[3] Randomised trials have demonstrated that a reduction in salt intake lowers BP in both hypertensive and normotensive individuals, in both adults and children.[4,5,6] There is also compelling evidence that a lower salt intake is associated with a reduced risk of CVD and total mortality.[7 8] Indeed, salt reduction is one of the most cost-effective measures to prevent hypertension and CVD.[3 9] The World Health Organisation (WHO) has recommended a 30% reduction in population salt intake by 2025, and also set a target of <5 g/d for all adults and lower levels for children.[10] Many developed countries have started salt reduction initiatives.[11] Salt intake has been successfully reduced in Finland and the UK, accompanied by falls in population BP and CVD mortality.[12] Developing countries, however, are lagging behind. China is the largest developing country with one fifth of the world population. Salt intake in China is very high with an average of 12-14 g/d in adults[13-15], and in some rural areas of northern China, salt intake could be as high as 18-20 g/d.[16] Approximately 80% of the salt in the Chinese diet is added by the consumers during cooking or in sauces.[17] It is extremely challenging to reduce salt intake in such settings due to the difficulty in changing individuals' dietary behaviours. Our previous study (School-EduSalt, **School-**based **Edu**cation programme to reduce **Salt**) has developed a novel and effective approach to reducing salt intake in northern China.[13] In School-EduSalt, primary schoolchildren aged ≈10 years were educated about the harmful effects of salt on health and how to reduce intake during the school's usual health education lessons. Children then instructed their families to reduce salt. The results showed that, over one school term (≈3.5 months), salt intake was reduced by

≈25% in both children and adults as measured by 24-hour urinary sodium excretion. The reduction in salt intake led to a significant fall in systolic BP of 2.3 mmHg in adults.[13] It was estimated that, if School-EduSalt was implemented and sustained, it would prevent ≈400,000 stroke and heart attack events per year in China.

Previous studies have shown that salt reduction achieved by dietary advice attenuates over time and maintaining a lower salt intake long-term remains a challenge.[4] The School-EduSalt was successful over one school term of ≈3.5 months. The question is how to continue and reinforce the salt reduction education to achieve a sustainable, progressive lower intake to achieve the WHO's target.

Mobile technology is increasingly used in health education.[18] Recent studies have suggested that game-based intervention has great potential in changing behaviours due to the popularity of gaming.[19] China has the largest and fastest growing mobile internet population with 802 million people using internet and mobile phone penetration reached 98.3% of the population by June 2018.[20] Mobile-based decision support system has been shown to be effective in increasing medication use in individuals with high CVD risk in rural China.[21] Our team have recently developed a smartphone app (KnowSalt) which can be used by individuals to estimate their salt intake and the major sources of salt in the diet. The methodology underpinning KnowSalt app had been validated in a pilot study in primary schoolchildren and their families.[22]

Our proposed study building upon School-EduSalt and KnowSalt app will develop an innovative smartphone application focusing on salt reduction (AppSalt) through functional modules of education, evaluation, target setting and monitoring, decision support and management, with the aim of reinforcing School-EduSalt to achieve a progressive lower salt intake for long term. To evaluate the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised trial.

## METHODS AND ANALYSIS

The project consists of 2 phases: (1) Developing AppSalt platform; (2) Carrying out a cluster randomised controlled trial.

## Phase 1 – Development of AppSalt platform

AppSalt platform comprises a smartphone app named AppSalt (family end) and a WeChat mini app (teacher end). The AppSalt consists of 4 core procedures (i.e. Education, Evaluation, Decision support and Reminding) and 3 supportive modules (i.e. Competition & Award, Supervision & Communication and SaltSwitch) (Figure 1).

***Core procedures***

1. "Education" is to educate the families about the harmful effects of salt on health and how to reduce salt intake. Nine lessons are developed, each starting with a 10-min lecture on salt reduction, followed by a few questions to test whether the families have understood the content. At the same time, the questions and answers will re-enforce the key messages. Following each lesson, the families are required to complete a practical session which is designed to help the families to prepare foods with reduced salt at home and to choose lower-salt foods when shopping.

2. "Evaluation" is to estimate salt intake and the main sources of salt for every member of the family. After completing a simple questionnaire, the family will be provided with the information on the top 3 contributors of salt in their diet. This will help the family make a decision on how to effectively reduce salt intake. Evaluation of the top 3 contributors (i.e. top 3 sources of dietary salt) will be based on a 7-day salt surveillance method. Participants will record frequency of dining out, consumption of processed foods and the amount of salt added during cooking. The added salt will be assessed by weighing salt, soy sauce and other primary salty condiments on the first and last day of the evaluation period.[23]

3. "Decision Support" will set target for total salt intake and specific targets for top 3 contributors. Lower-salt sample recipes and specific measures, e.g. reducing the amount of salt used during cooking by 50%, will be recommended. The recommended measures will be customised as an action plan.

4. "Reminding" will remind the family how far their salt intakes are away from the targets set and highlight further action plans.

***Supportive modules***

1. The "Competition & Award" module will help the participants to find out their own ranking position assessed by salt intake level and the extent of salt reduction among all participants (NB: only their own ranking will be displayed and other participants' ranking will not be revealed to them). The family with the lowest salt intake and the family who achieve the greatest reduction in salt intake, will be the winners of competition. They will be awarded an honorary title like "Salt Reduction Pacesetter" and get a small gift.

2. "Supervision & Communication" module: The teachers and researchers will use the function "Supervision" to announce instructions, newsletters, and school canteen menus, as well as providing answers to any queries. The participants will use the function "Communication" to ask any questions and also to exchange experience and knowledge with other participants.

3. The "SaltSwitch" module will help the participants to choose pre-packaged foods with lower salt. "SaltSwitch", as a sub-function of "FoodSwitch"[24] integrated into the AppSalt, has a database of over 50,000 pre-packaged foods collected by the George Institute China. By scanning the barcode of the pre-packaged foods, the "SaltSwitch" will provide information on salt/sodium content and compare it with other similar products based on products' labelling.

AppSalt will be installed in the smartphone of adult family members. Children are only allowed to use AppSalt accompanied by their adult family members to complete AppSalt core procedures as required. New features with a variety of presentation styles on salt reduction education will be added to keep the programme attractive to the participants.

The school teachers will use the WeChat mini app (teacher end) to send messages to the families, provide timely feedback to any queries, and check families' progress and ensure all families complete the procedures in time. The teachers will also report any issues to the site managers and the research team where appropriate.

## Phase 2 ─ Cluster randomised controlled trial (RCT)

To test the effectiveness and cost-effectiveness of the AppSalt programme, we will carry out a cluster randomised controlled trial (Figure 2).

***Study Setting and participants***

Considering the geographical location, economic level and dietary habit, our study will be undertaken in selected primary schools from urban and rural areas of 3 provinces in northern (Hebei), central (Sichuan) and southern (Hunan) China.

To recruit schools, we will firstly contact the local education authority through local Health/Education Bureau or Centre for Disease Control (CDC) to gain their opinion, support and approval. We will then contact schools' head-teachers to request their participation in the study. In each school, there are 6 grades with age ranging from 7 to 12 years and our study will be carried out in grade 3 (age 8-9 years). Head-teacher will choose one class whose teacher in charge is willing to collaborate with the researchers. From each class, we will randomly select 11 children and 22 adult family members (i.e. 1 child and 2 adults per family) for evaluation. The inclusion criteria are (1) Children and their adult family members have to eat homemade meals at least four times per week; (2) One of the adults in the family has a mobile device with access to Internet; (3) If more than 2 adults in one family agree to take part in the

evaluation, we will select two in the order of grandparents, parents, uncles and aunties; (4) Participants have been local residents for over 6 months, without moving plan within 24 months. We will exclude the individuals who cannot or refuse to collect 24-hour urine.

***Randomisation***

Schools (clusters) will be randomly assigned (1:1) to either the intervention or the control group. Randomisation will be stratified by the location of schools (i.e. south or north, urban or rural) and the size of the class. The randomisation will be carried out using computer generated random number by an independent statistician who is blind to the identity of the schools. The randomisation will take place after baseline data collection has completed. Therefore, the participants, school-teachers and local investigators who undertake recruitment and data collection, will be unaware of the allocation until the point prior to the commencement of the intervention.

***Intervention***

Our goal is to lower salt intake (measured by 24-hour urinary sodium) by a minimum of 15% (≈1.5g salt) for both children and their families. To achieve this goal, a strategy towards a 50% reduction should be implemented. To make the decision-support algorithm simple in the AppSalt, we will set targets for the top 3 contributors to salt intake, such as cooking salt. Targets and priority actions will be individualised depending on the sources of salt in the individual's diet which will be provided by AppSalt. During the education lessons delivered through AppSalt, the participants will be taught the methods on how to effectively reduce salt intake, e.g. reducing the amount of salt, soy sauce and bean paste used during cooking. Garlic, ginger and herbs are recommended for enhancing food flavour. We also recommend replacing pickles with fresh vegetables, and replacing salted eggs and peanuts with unsalted ones.

In the intervention group, the AppSalt intervention package will be delivered to all children and their families in the whole class, despite only 11 children and their families being

randomly selected for evaluation. The adult family members will be authorized to install and operate the AppSalt programme, while children will be assigned homework to get the whole family to reduce salt with the support of AppSalt. Children's homework will include: (a) helping the family to set salt reduction target and reminding the whole family of this target on a regular basis; (b) getting the whole family involved in salt reduction activities and persuading the person who does the cooking to reduce the amount of salt used during food preparations at home; (c) working with their family members to complete the AppSalt core procedures, including education, evaluation, target setting and monitoring. In addition to the online lessons, school teachers will organise three face-to-face seminars for both children and adults during the one-year intervention period. This will provide an opportunity for the participants to share experiences and discuss challenges and solutions. These seminars will be integrated into the schools' routine parent meetings.

Trained teachers will provide guidance on AppSalt utilisation, assign and check children's homework including monitoring the progress of salt reduction. They will also create salt-reduction environment, e.g. putting up posters in classroom, campus and canteens. The AppSalt will be activated at the beginning of the intervention for all families in the intervention group. Throughout the study, participants will receive salt reduction messages and newsletters via AppSalt on a monthly basis. Participants will be encouraged to use AppSalt and communicate with the teachers and other families to share experiences. The mandatory tasks for the participants include completing the online lessons and the related Q&As (Questions and Answers) at baseline and every month thereafter, and completing the core procedures, i.e. salt intake estimation, target setting at baseline and every 3 months thereafter. In addition to the mandatory tasks, the participants are encouraged to repeat the core procedures as often as they wish, in order to monitor their progress and achieve progressive reductions in salt intake. Based on the progress monitored from the WeChat mini

app, the teachers will remind children that they should complete their homework which is to help the family complete the AppSalt procedures in time and to instruct the family members to reduce salt to the target.

The records from AppSalt, e.g. salt intake and how far the intake is different from the target set, will be used to monitor compliance. During follow-up, the participant who fails to achieve the salt reduction target, will be sent a specially designed message via AppSalt and a letter to the child through his/her teacher to remind the family of the salt reduction target.

The intervention duration is 2 school terms, i.e. 1 year. Children in the control group will carry on with their usual health education lessons as in the curriculum. After the trial is completed, we will introduce the AppSalt to all schoolchildren and their families including those in the control group.

***Sample size calculation***

Based on the School-EduSalt trial,[13] assuming a standard deviation of 24-hour sodium excretion is 85mmol/day, and intraclass correlation coefficient (ICC) is 0.05, we estimate that a sample size of 594 children from 54 schools (18 primary schools from each province in both urban and rural area, and 11 children per school) would provide a power of 80% (with a two-sided alpha=0.05) to detect a difference in mean 24-hour urinary sodium ≥26mmol/day (1.5 g/d salt) between intervention and control group, allowing for a 15% drop-out rate of participants. We aim to recruit 2 adults per family, therefore 1188 adults will be recruited into the study for evaluation.

***Outcome measures***

The primary outcome is the difference between the intervention and control group in the change of salt intake as measured by 24-hour urinary sodium from baseline to the end of the trial. The secondary outcome is the difference between the two groups in the change of systolic BP for adults.

***Outcome assessments***

All outcome measurements and assessments will be carried out at baseline and at the end of the trial in exactly the same way in all schools for all participants, irrespective of their assignment to intervention or control group.

Two consecutive 24-hour urine collections will be made at each time point, using the stringent protocol which we developed in the School-EduSalt study.[13] Although there are other more convenient methods for assessing salt intake, e.g. a food diary, they are not reliable, and the most accurate method is 24-hour urine collection.[25] Our previous studies have shown that it is entirely feasible to collect 24-hour urine in both children and adults.[13] The participants will be carefully instructed on how to accurately collect 24-hour urine by trained research staff. On the first day, the participants will be asked to come to the schools. The researchers will ask the participants to empty bladder and discard the urine. The researchers will record the start time and date of the 24-hour urine collection. They will then give the participants the collection equipment including containers and collection aids such as carrier bags. The participants will be instructed to collect all subsequent urine voids over the next 24-hour period. On the second day at the same time, the participants will be asked to bring the urine collection bottles back to the schools and they will be asked to pass the last urine into the container. The researchers will record the finish time of the first 24-hour urine collection. The researchers will then give the participants the collection equipment for the second 24-hour urine collection and repeat the process. During the 24-hour urine collection period, the participants will be asked to take spare urine containers with them when they go to school or work. Spare collection equipment will also be available in the schools, in case children forget to bring them. In the case that the participant misses one or more urine voids or spillage occurs, the participant will be asked to do a further 24-hour urine collection. The 24-hour urine collections will be made either at weekdays or at weekends. For each

participant, the 24-hour urines will be collected on the same days of the week for baseline and for follow-up at the end of the trial.

We will measure urine volume, sodium, potassium and creatinine. Ion-selective electrode method will be used for sodium and potassium analysis and enzymatic method for creatinine assay. 24-hour urinary creatinine together with urine volume will be used to determine if the collection is likely to be complete. The biochemist who performs the measurements of urinary electrolytes will not be told which group the participant is allocated.

In addition to 24-hour urine collection, we will measure BP and heart rate using a validated automatic machine with the appropriate size of cuff. Three readings will be taken in the right arm at 1-2-minute intervals at sitting position after the participant has had 10 minutes' rest in a quiet room. Body weight, height and waist circumference will also be measured. Survey on Knowledge, Attitude and Practice (KAP) related to salt will be completed via questionnaire.

## Data collection, management and analysis

### *Data collection*

Our study will have two major data outputs. One is the "App Data" generated automatically when the AppSalt platform is used by the families in intervention group to support salt reduction. The App Data include information on demographic characteristics, eating habits, amount and sources of salt in the diet, as well as information (or App logs) on the use of AppSalt. The other data output is the "RCT Data" which is generated by both intervention and control groups during the RCT. The RCT Data will be collected through a specially designed mobile device based electronic data capture system (mEDC) by well-trained field investigators. The mEDC has been validated and widely used in other clinical trials[26] with more advantages on process and quality control compared with traditional EDC. The RCT data include information on demographics, social-economic information, KAP, measurement of height, weight, waist circumference, BP, heart rate, 24-hour urine volume and electrolytes,

as well as information on costs for all the components of intervention conducted through the AppSalt programme.

***Data management***

All cleaned and locked datasets together with the study design, questionnaire, code list and definition of database and variables will be stored with a unique ID number attached but no personal identifiers, in The George Institute China (TGI), following an established standard operating procedure for data security. To guarantee the data security, the mobile app developer (i.e. the IT team at Beihang University) must follow the "Mobile Application Information Service Regulation" issued by the Cyberspace Administration of China in 2016. Although personal data are accessible to app developer, disclosure of such information is prohibited. In addition to the development and maintenance of the AppSalt and mEDC, IT team will also provide data management service during the study to guarantee the safety, integrity and proper use of the data collected through AppSalt and mEDC.

***Statistical Analysis***

Data analyses will be performed according to the intention-to-treat approach. The effect of the intervention on the outcomes will be tested using linear mixed models with participants nested within family units and families nested within schools. We will include group (intervention, control), time (baseline, end of trial), and time×group interaction, with the time×group interaction term indicating differential change by group from baseline to the end of the trial. We will adjust for the stratification variables at randomization and potential confounding variables. Various sensitivity analyses will be carried out to examine the robustness of the conclusions of the primary analysis. Results will be reported as mean, SD, SE, and 95% confidence interval where appropriate. All analyses will be two sided and $P<0.05$ is considered significant. SAS will be used for the analyses.

***Economic evaluation and process evaluation***

Economic evaluations will be carried out from health sector perspective to compare the m-Health strategy with usual care and it will entail two components: a trial-based economic evaluation and a modelled economic evaluation of long-term costs and outcomes. Intervention costs will include those in running the programme but exclude any research and development costs. The trial-based economic evaluation will be assessed initially in terms of incremental cost per unit reduction in salt intake and systolic BP. The modelled economic evaluation with discounting will examine the cost, survival, quality of life over lifetime, via capturing various health states (including death and CVD events) to estimate incremental cost per life year saved and cost per Quality-Adjusted Life Year (QALY) gained. The transition probabilities across health states and costs attached to various health states will be based on literatures and the long-term effects of the reduction in salt intake or systolic BP will be derived from the trial findings and/or literatures of disease progression. Sensitivity analyses will be carried out to estimate uncertainty about the primary findings associated with varying key parameters.

Mixed-method process evaluations will be conducted during and at the end of the study using data from AppSalt, key informant interviews with researchers and teachers, and focus groups interviews with participants. This will help understand the barriers and facilitators of the intervention as well as the acceptance and effect of the AppSalt programme.

**Project status and timelines**

Recruitment of schools and participants started in September 2018. Baseline assessments were carried out between September and December 2018. As the intervention duration is one year, the final follow-up assessments will be carried out between September and December 2019.

**Expected outcome and potential impact**

The study will provide a novel, feasible and effective approach to achieving a sustainable

reduction in salt intake in both children and adults. The use of AppSalt platform in delivering health education lessons is particularly advantageous over the traditional school education method in terms of reducing the burden on teaching staff. Furthermore, our study covers a wide range of the population (children and adults, rural and urban, north and south), the results should therefore be generally applicable to the whole Chinese population. If the programme is implemented and sustained across China, it will reduce population salt intake and thereby prevent hundreds of thousands of strokes, heart attacks and heart failure each year, and lead to major cost-savings to individuals, their families and the health service. Although our study will be carried out in China, the AppSalt programme could potentially be adapted by many other countries. Additionally, our model on salt reduction could possibly be adapted for other dietary and lifestyle changes to prevent CVD and other non-communicable diseases, which will have major public health implications.

## Patient and Public Involvement

During the development of the study protocol, we had 2 round-table meetings with 6 head-teachers from 3 different cities and several telephone meetings with teachers and children's parents to gain their opinion, particularly on the feasibility of carrying out the study in school settings and how to incorporate the intervention programme into the school curriculum. During the study, school teachers will assign and check children's homework. Both teachers and head-teachers will be informed of the study progress by monthly communication via newsletters, WeChat and website. Upon completion of the study, we will disseminate the results to head-teachers, teachers, children and their parents. We will also discuss with them and other stakeholders on how to translate research findings into practice.

## ETHICS AND DISSEMINATION

The study has been approved by Queen Mary Research Ethics Committee in the UK (QMERC2018/13) and Peking University IRB in China (IRB00001052-18051). Written

consent will be obtained from all participants according to well-established practices. For children, participant assent and parental written consent will be obtained. All participants will be free to discontinue their participation at any time with no explanation required.

The findings of this study will be disseminated widely through conference presentations, peer-reviewed publications, press release and social media. Furthermore, the results will be disseminated worldwide through World Action on Salt and Health[27] which is a global non-profit organisation with 600 members from 100 countries with the mission to improve the health of populations by reducing salt intake.

**Authors' contributions:** FJH and PZ conceived the project and contribute equally to the work. FJH, PZ, YLi and RL designed the study and oversaw the conceptualisation and development of the app. PZ, YLi, RL, FC, YZ, WZ, DL, HC, TW, JY, JL and SZ facilitates Patient and Public Involvement and were responsible for setting up the study in each site. YLiu and RL are leading the development and maintenance of the app. XL and CW contributed to sample size calculation and analysis plan. All authors contributed to the development of the intervention and evaluation. FJH wrote the first draft of the manuscript, and PZ, YLi, RL, CW and GAM revised the draft. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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**Competing interests**: FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH and Chairman of WASH. BPUK, CASH and WASH are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. Other authors declare no competing interests.

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**Word Count**: 4076 words.

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# Figure Legends

**Figure 1.** AppSalt core procedures and modules.

**Figure 2.** Appsalt trial design. BP: Blood Pressure.

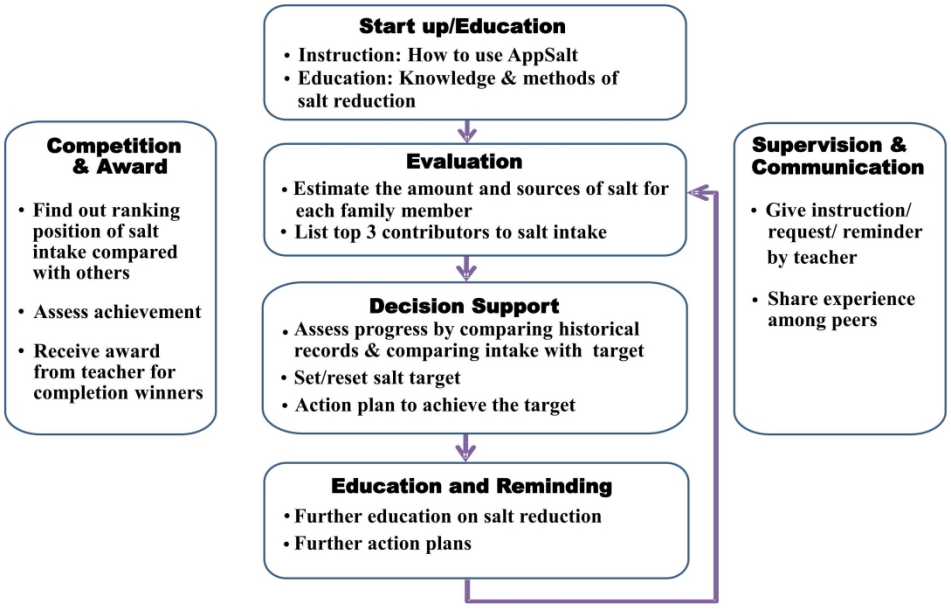


Figure 1 AppSalt core procedures and modules.

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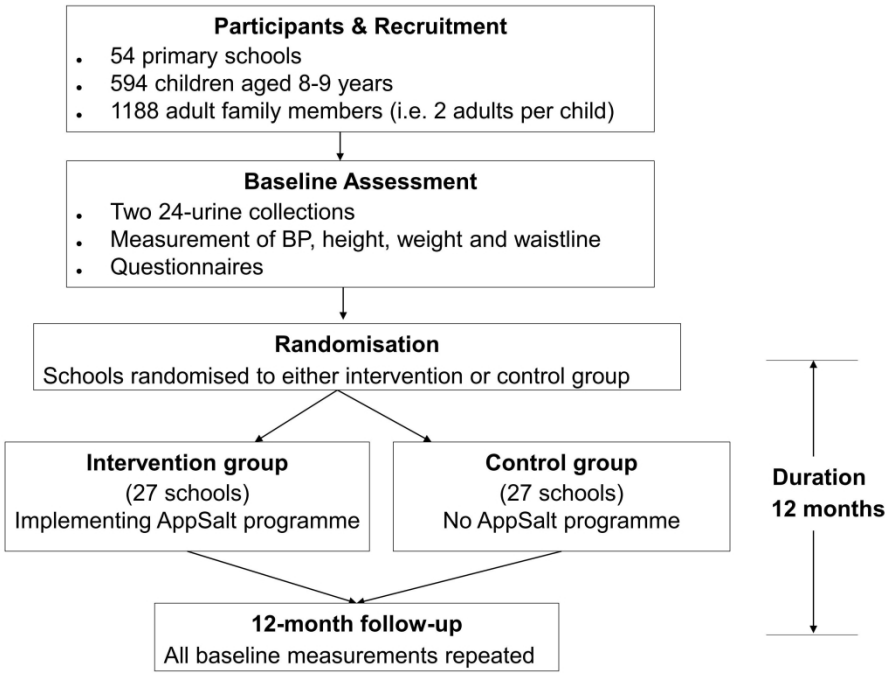


Figure 2 Appsalt trial design. BP: Blood Pressure.

277x189mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym<br>**An app-based programme to reinforce and maintain lower salt intake (AppSalt) in schoolchildren and their families in China Protocol of a cluster randomised controlled trial** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br>**ChiCTR1800017553** |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br>**Yes** |
| Protocol version | 3 | Date and version identifier<br>**N/A** |
| Funding | 4 | Sources and types of financial, material, and other support<br>**Page 17** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br>**Page 17** |
| | 5b | Name and contact information for the trial sponsor<br>**Queen Mary University of London** |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities<br>**None** |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)<br>**N/A** |

| | | |
|---|---|---|
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Page 4-5** |
| | 6b | Explanation for choice of comparators **Page 11-13** |
| Objectives | 7 | Specific objectives or hypotheses **Page 9** |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Page 8-11** |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Page 8-9** |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Page 8-9** |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Page 9-11** |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **N/A** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Page 10-11** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial **N/A** |

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| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended<br>**Page 11-13** |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)<br>**Page 15** |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations<br>**Page 11** |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size<br>**Page 8** |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions<br>**Page 8-9** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned<br>**Page 8-9** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br>**Page 9** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br>**Page 13** |

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|---|---|---|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br>**N/A** |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol<br>**Page 13-14** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols<br>**Page 7-8** |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol<br>**Page 13-14** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol<br>**Page 14** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br>**Page 14** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)<br>**Page 14** |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed<br>**N/A** |

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| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial<br>**N/A** |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct<br>**N/A** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br>**N/A** |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br>**Page 16-17** |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)<br>**Page 16-17** |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br>**Page 16-17** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br>**N/A** |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial<br>**Page 13-14** |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br>**Page 17** |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators<br>**Page 13-14** |

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|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation<br>**N/A** |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions<br>**Page 16-17** |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br>**N/A** |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br>**N/A** |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br>**Available Upon Request** |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable<br>**N/A** |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-5 |
| | 2b | Specific objectives or hypotheses | 9 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6-10 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 8-9 |
| | 4b | Settings and locations where the data were collected | 8-9 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-13 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 11 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 9 |

| | | | |
|---|---|---|---|
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 13 |
| | 11b | If relevant, description of the similarity of interventions | Not applicable |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 14 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 14 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Not applicable |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | Not applicable |
| | 14b | Why the trial ended or was stopped | Not applicable |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Not applicable |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Not applicable |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Not applicable |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | Not applicable |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Not applicable |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | Not applicable |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 3 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 15-16 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 15-16 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 2 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Not applicable |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 17 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.